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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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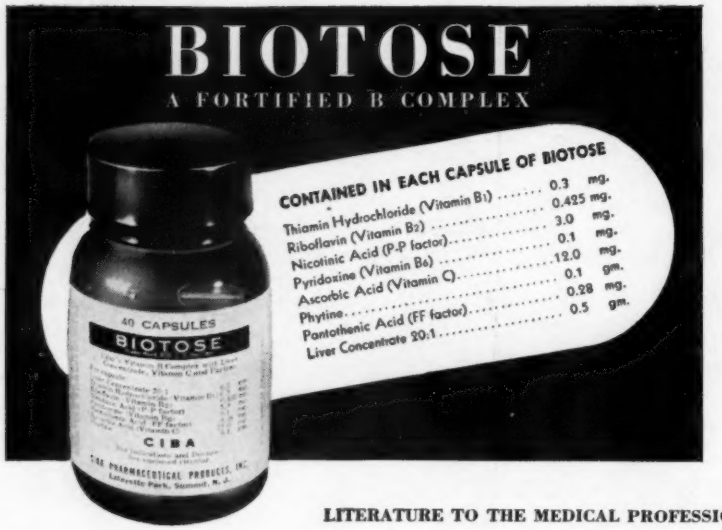
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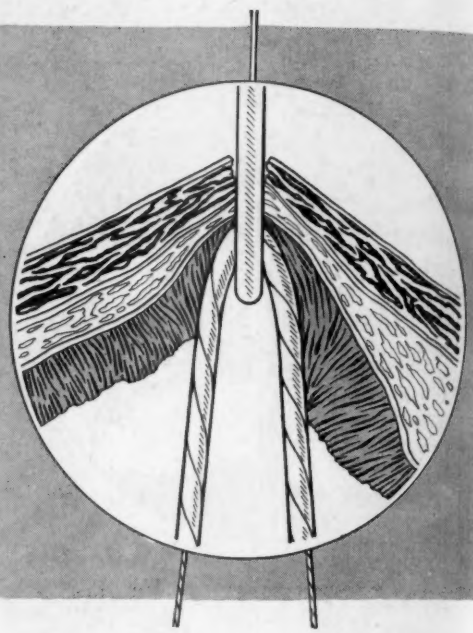

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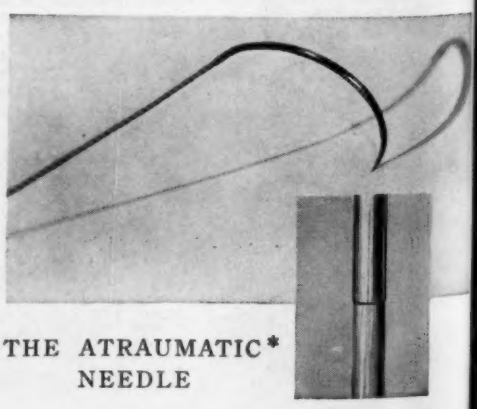

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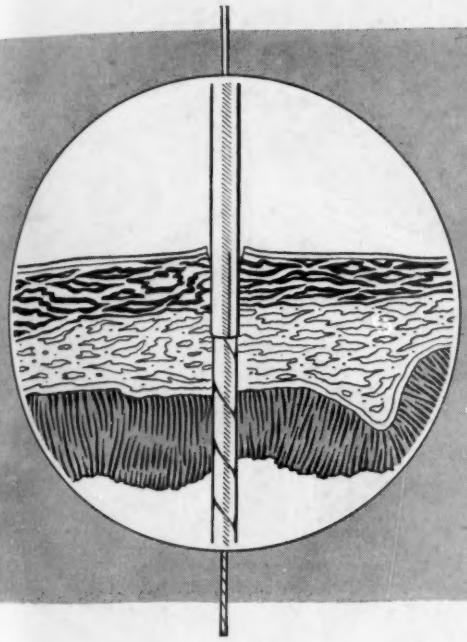

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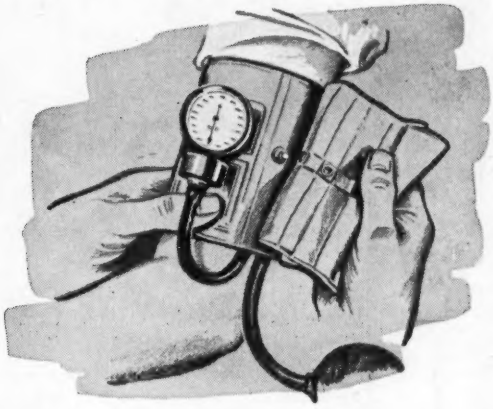

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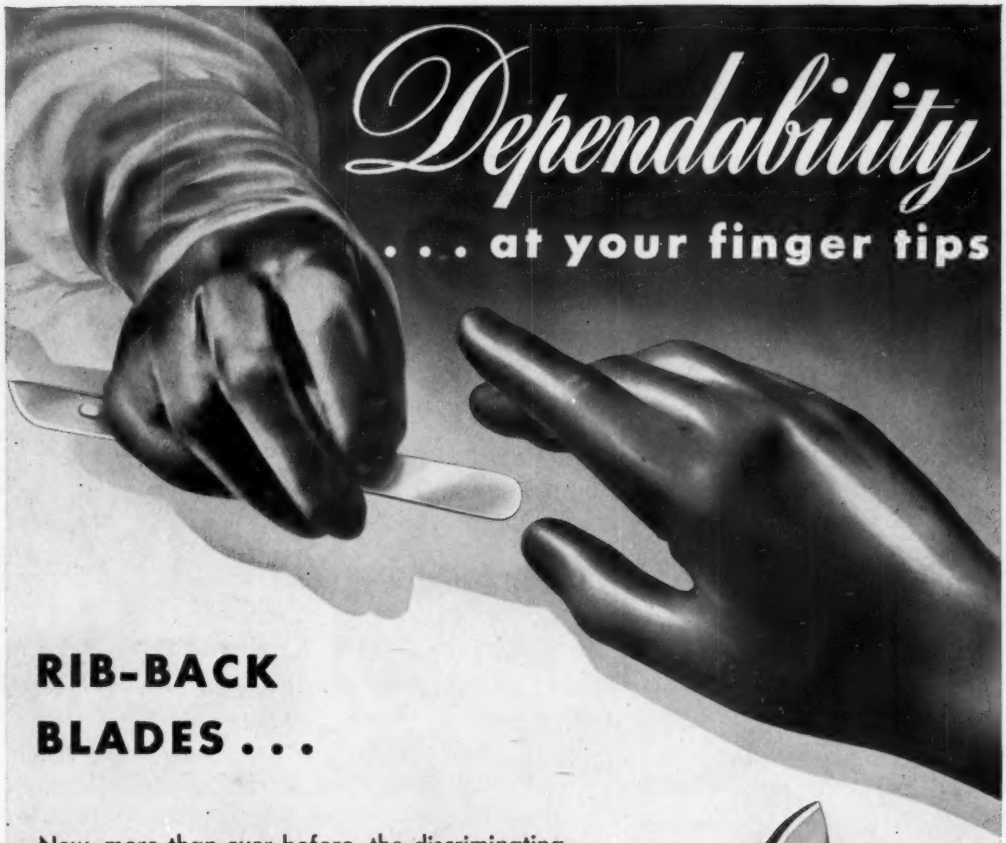

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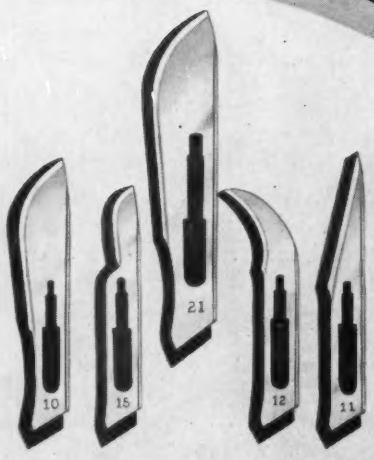

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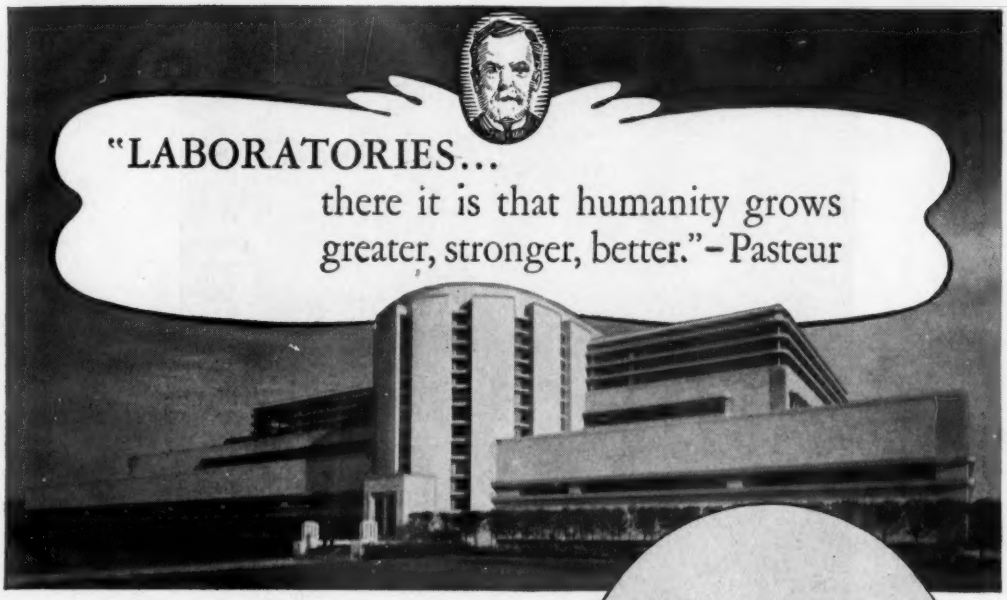

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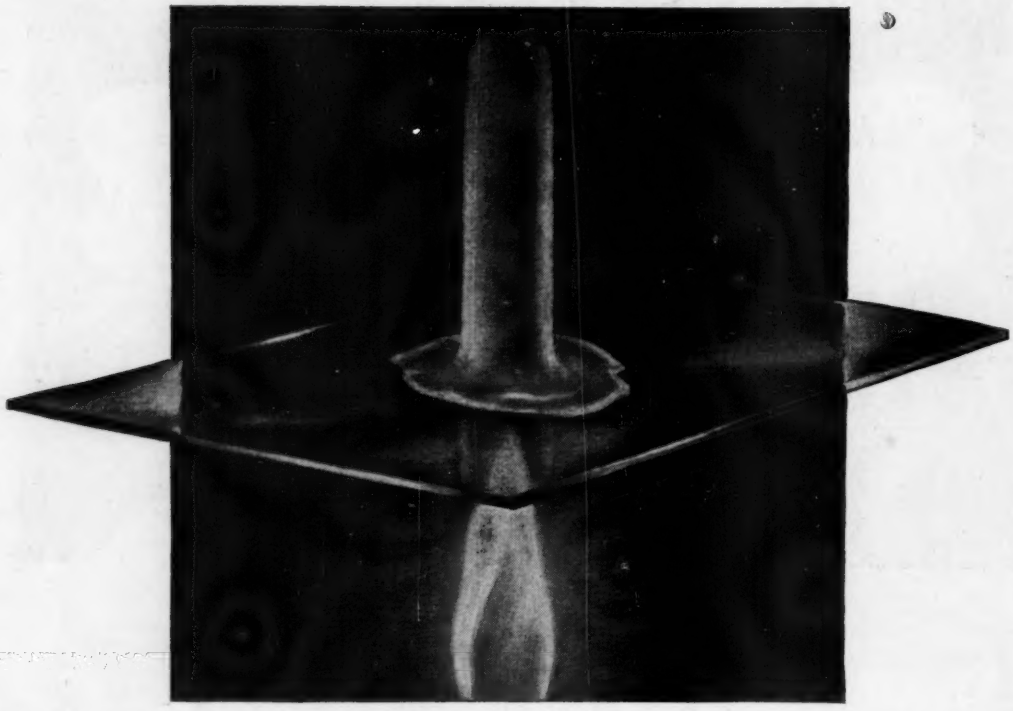

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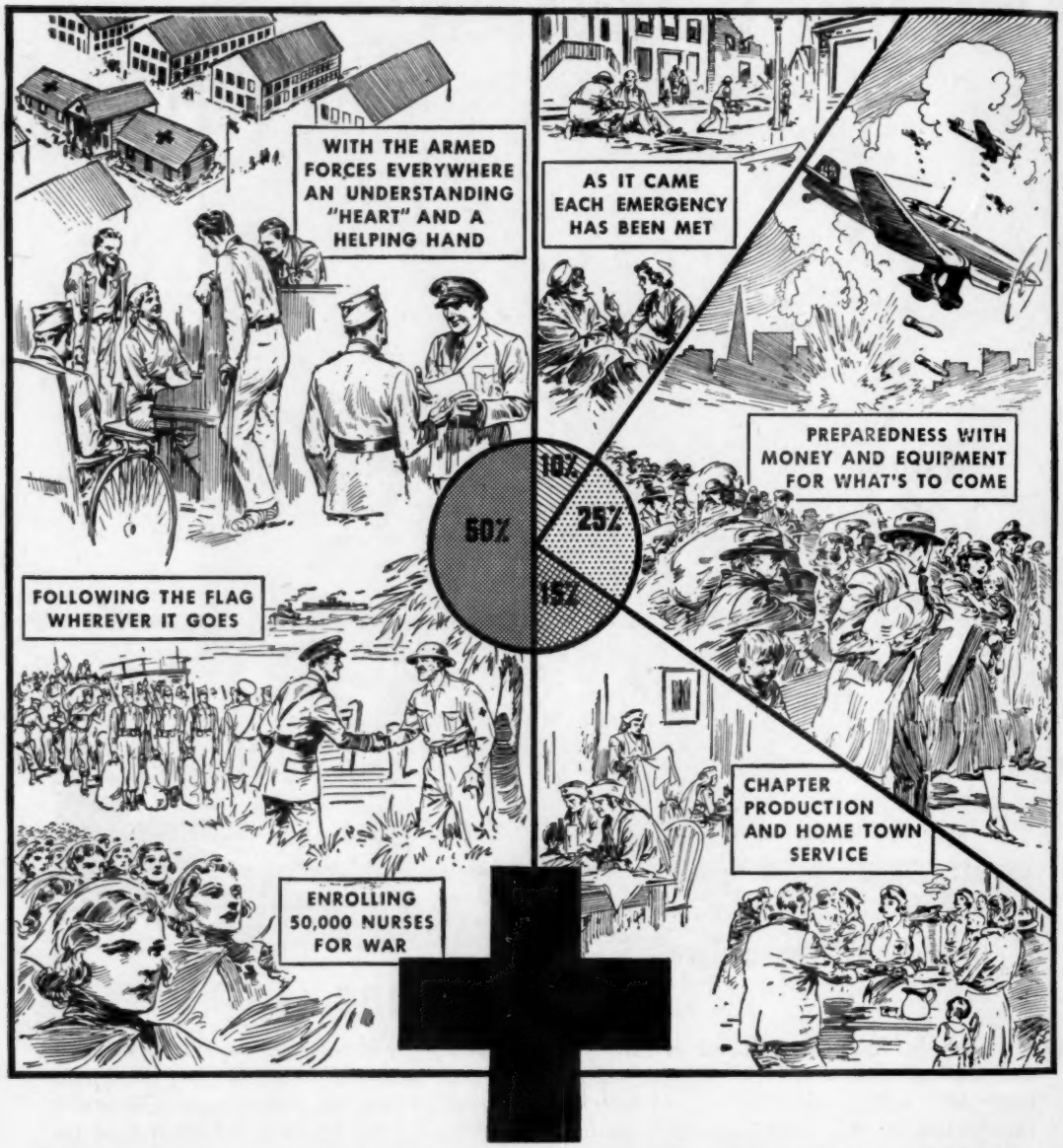
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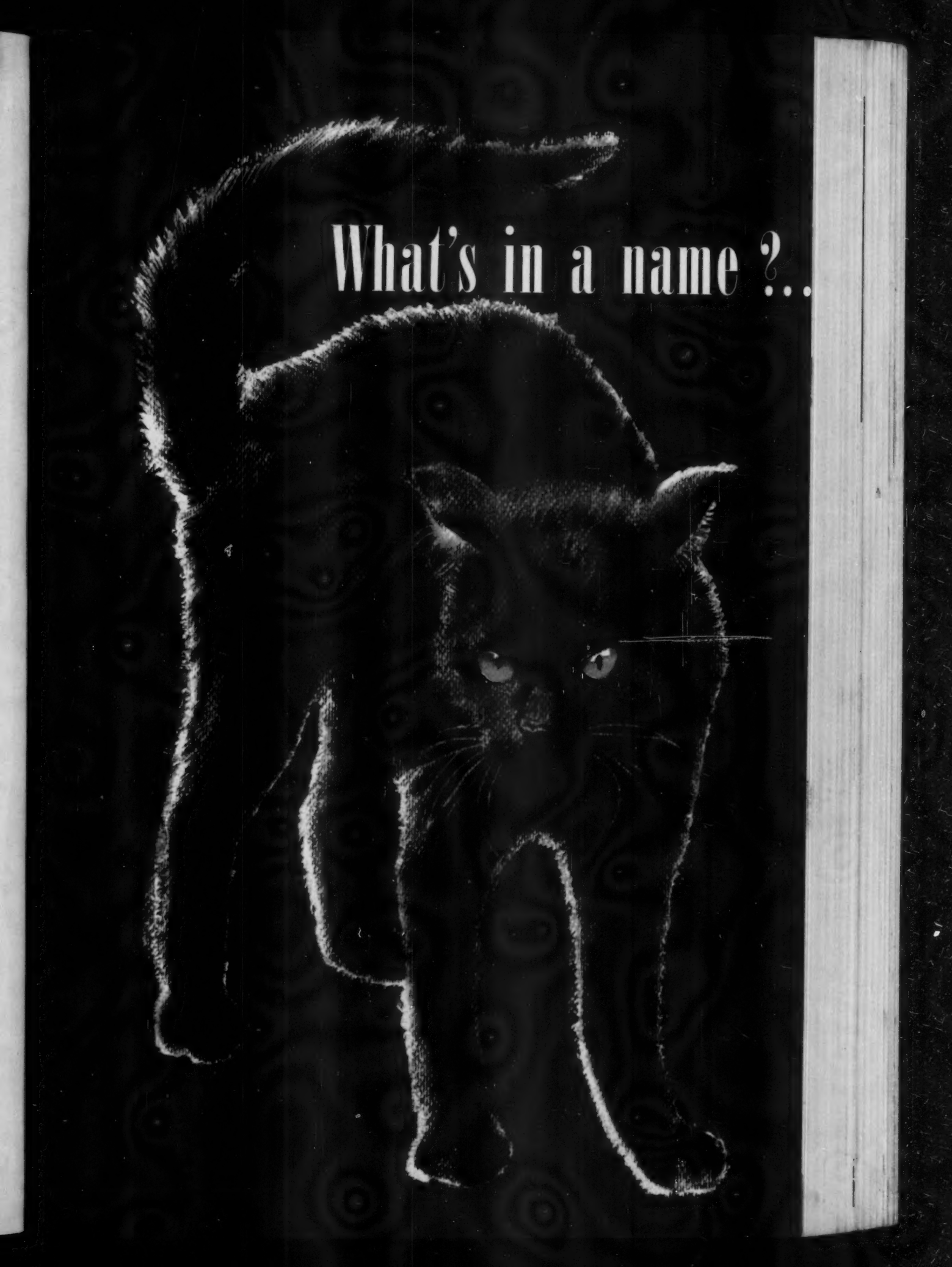
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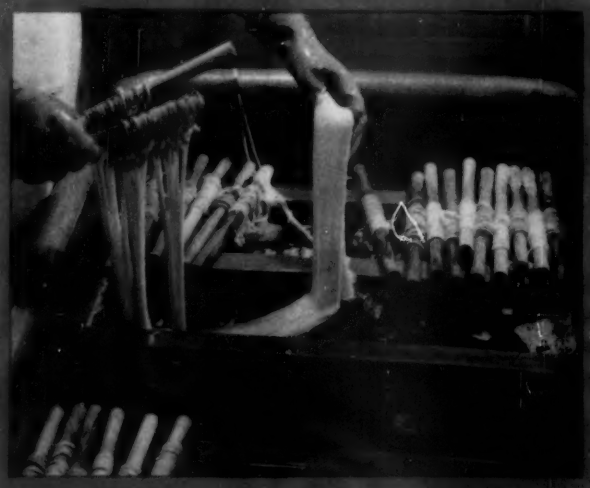

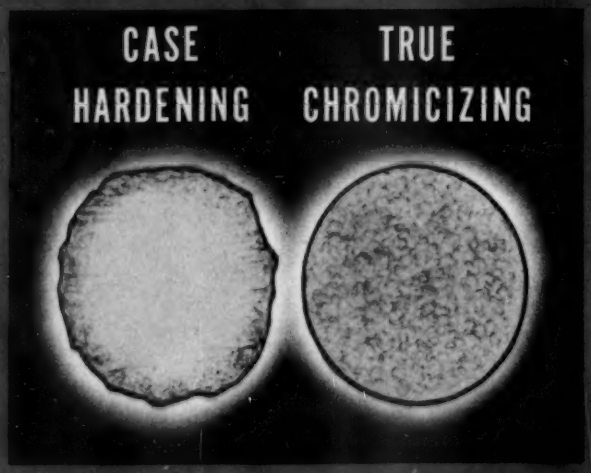

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SURGERY

VOL. 12 NOVEMBER, 1942 No. 5

Original Communications

THE FLOW OF LYMPH FROM BURNED TISSUE, WITH PARTICULAR REFERENCE TO THE EFFECTS OF FIBRIN FORMATION UPON LYMPH DRAINAGE AND COMPOSITION

WILLIAM W. L. GLENN, M.D., DELORES K. PETERSON, B.S., AND CECIL K. DRINKER, M.D., BOSTON, MASS.

(From the Department of Physiology of the Harvard School of Public Health)

THE PROBLEM

IN A SERIES of papers summarized in 1938, Menkin[1] presented the idea that inflammatory processes differ in their tendency to spread, in relation to the local irritation they have caused. Inflammation has as its simplest elements, first, a great increase in capillary permeability, which floods the tissues with a slightly diluted blood plasma containing fibrinogen and prothrombin; second, a variable amount of tissue injury; and, third, migration of leucocytes. The last of these three features of inflammation is of little importance to the subject matter of this paper.

Menkin believed that lymphatic blockage by thrombosis and the conversion of the extravascular milieu into a fibrinous clot are of paramount importance in checking the spread of inflammation. The formation of fibrin lymphatically and extravascularly is due to the free escape of fibrinogen and prothrombin from the blood capillaries and the release of thromboplastic substances from injured cells. Menkin,[2] 1935, summed up the issues involved as follows: "Powerfully necrotizing irritants produce as a result of an increase in capillary permeability and of lymphatic damage, an extremely prompt reaction, perhaps best termed *fixation*. By this process, the area of injury is mechanically circumscribed and the dissemination of the irritant is prevented. *Staphylococcus aureus* is an example of such a bacterial irritant.[3] Aleuronat

Received for publication, April 16, 1942.

is a chemical irritant of similar potency. Mild irritants, on the other hand, produce only a delayed reaction, thus allowing relatively free penetration of the irritant into the circulation for a considerable interval of time. Occlusion of the draining lymphatics in such instances often takes place as late as two days subsequently to the inoculation of the irritant. Hemolytic streptococci exemplify this type of irritant."

These very fundamental conceptions rest upon persistent and arresting experimentation carried on over many years. The point to be borne in mind is not that inflammation is of itself circumscribed, but that the destructive character of the inflammatory agent is extremely important in the localizing process. The more nearly invading organism and host are compatible, the more readily the invader spreads. If, however, the irritant causes cell destruction and outpouring of plasma from blood capillaries, then extravascular coagulation begins at once and the whole extravascular environment becomes a blood clot, which extends into the lymphatics. If blood capillaries are open through such regions, they will perform their functions of delivery and absorption of water and solutes. But lymph drainage with gradual spread of bacteria, viruses, or certain poisons will become negligible.

The relation of these generalizations to the problem of burns reached us through experiments by Field, Drinker, and White,[4] 1932, who anesthetized dogs with nembutal, cannulated a lymphatic from a hind foot, and then immersed the foot in boiling water for two minutes, thus causing a very severe burn. Swelling began at once and there was an enormous outpouring of fluid from the blood capillaries which entered the lymphatics. Eventually a lymphatic end pressure developed which was that of the diastolic pressure of the blood. Lymph flowed freely from such a severely injured part during many hours.

There is an apparent disagreement between this last finding and the idea that the severity of injury and the restriction of lymph drainage correspond. Since burns have become a major problem in the present war and the issue of drainage from them of great moment, we have undertaken experiments to study lymph flow from tissues severely burned by surface scalding, the extent of lymphatic blockage and extravascular deposition of fibrin, and the possibility of shutting off lymphatic drainage by causing coagulation of all the fibrinogen escaping from the blood capillaries.

THE TECHNIQUE

In burns, the problem of selecting a standard procedure which can be applied comparatively to animal after animal is not so puzzling as in the case of surgical shock, but is of equal importance.

The Standard Burn.—After consideration, it was decided to use the simple method of Field, Drinker, and White,[4] 1932, namely, dipping the foot of a dog, anesthetized with nembutal, into water at 100° C. for two

minutes. A burn so produced was severe. The overlying skin was porky and blanched except at the margin of the burn, where dilated, congested vessels were noted. Between the toes blisters formed in every case. The advantages of this procedure are: (1) It is susceptible to precise repetition from animal to animal, and in the different feet of the same animal. (2) Swelling is prompt and localized, and lymph can be collected from lymphatics immediately above the margin of the burn. (3) No break in the skin occurs for a number of hours, so that there is no external loss of fluid from the burn and no destruction of tissue not due to the burn itself. If burned tissue is a source of toxic substances, there is a maximal opportunity for their absorption. (4) It is easily possible to decrease and increase the amount of fibrin formation in the burned area, in the first case by intravenous heparin injections, and in the second case by subcutaneous infiltration of tissue extract immediately after dipping the foot in hot water and before swelling begins.

Examinations of Lymph.—It is a simple matter to cannulate lymphatics above the ankle joint in the hind legs and above the radiocarpal joint in the fore legs. If necessary, one can readily find vessels at higher levels, that is in the groin or at the base of the neck. Control specimens of lymph were obtained by gentle massage of the foot. After burning, lymph flowed spontaneously and in large amounts.

During prolonged collections of lymph, coagulation in the cannula was prevented by means of a wire with a small loop at the end, which could be inserted into the cannula to the neck. From time to time the loop was dipped in dry heparin, which dissolved in the lymph as it entered the cannula and steadily checked the annoyance of clotting. Lymph flow was measured volumetrically. Protein was determined refractometrically. Cell counts and changes in the color of the lymph were recorded as required, during experiments which lasted from 14 to 24 hours.

THE EXPERIMENTS

Immediately following the burn there was a spontaneous flow of lymph which increased rapidly over the first 3 to 6 hours and then diminished gradually during the next 20 hours. The protein percentage likewise increased sharply and this increase was maintained until the end of the experiment. Tissue fluid protein, when quantitated, was approximately the same as the lymph protein. This fluid was obtained by puncture of the burned and swollen part with a small needle. A short time after the puncture is made the fluid collected is grossly similar to the lymph, a clear fluid, tinged with hemoglobin and clotting quickly unless heparinized.

Fig. 1 shows the result of dipping the right front foot of a dog in boiling water for two minutes with the resulting lymph flow. The opposite foot was dipped in exactly the same way, but immediately after being removed from the hot water it was infiltrated subcutaneously with

tissue extract made by grinding fresh beef lung, adding physiologic salt solution, and centrifuging to dispose of bits of tissue. Two things are obvious. First, there is an enormous increase in lymph flow from the right foot (*1*, Fig. 1) and the protein content (*1*, Fig. 1) of the lymph rises to more than 4 per cent and stays at that level. After some hours the lymph flow begins to fall, in all probability signalling a liberation of thromboplastic material at the site of the burn, which causes a sufficient degree of general coagulation to block lymph drainage.

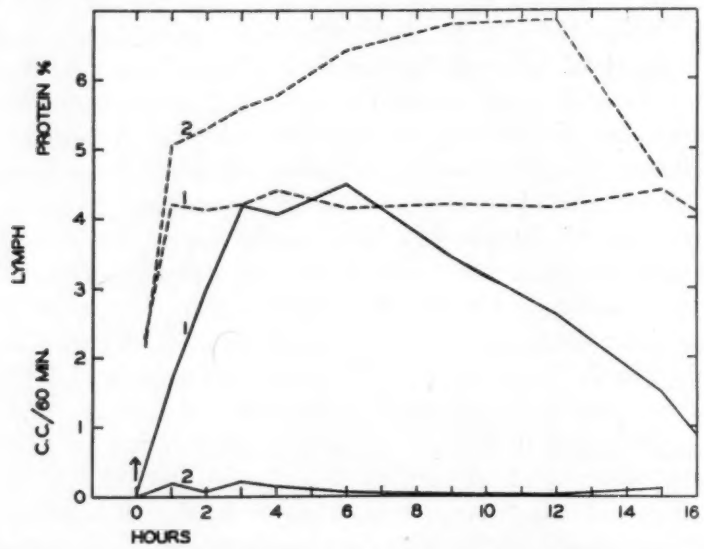

Fig. 1.—The effect on lymph flow and protein content of immersing the front feet of a dog in water at 100° C. for 2 minutes. Burn at the *arrow O. Curves 1 and 1,* for the right front foot, in the continuous line, show lymph flow in cubic centimeters per hour, and in the broken line the percentage of protein in the lymph during 16 hours following the burn. *Curves 2 and 2* are similar in construction but in this case, immediately after a similar burn of the left front foot, tissue extract was injected subcutaneously. The foot swelled enormously, but lymph flow was negligible, and the small amount collected had a very high protein content. *Ordinates,* lymph flow in cubic centimeters per hour and protein percentage in lymph. *Abscissae,* time in hours.

In the case of the left front foot, dipped in boiling water and then infiltrated with tissue extract so that coagulation was maximal, it is obvious that lymph flow is negligible (*2*) and lymph protein high (*2*, Fig. 1). If one makes sections of the skin and subcutaneous tissues from feet treated in the manner described, it is easy to show extensive fibrin formation in the foot burned and injected with tissue extract. The opposite foot, burned, but given no extraneous supply of thromboplastic material, shows a meager amount of fibrin on section and it is obvious that coagulation has been insignificant.

Fig. 2 is one of a number of experiments in which a foot was dipped in water at 100° C. for two minutes with the usual prompt and extensive increase in lymph flow. At the end of the third hour, when lymph flow had become very rapid and swelling was extensive, the burned area was injected subcutaneously with tissue extract. Lymph flow stopped

instantly, and during 12 hours was not resumed. Two other lymphatics from the region were cannulated during this time but no lymph could be collected.

Fig. 3 shows, above, the normal front feet of an anesthetized dog. The lower photograph is of the same feet 1 hour and 45 minutes after immersion in water at 100° C. for two minutes. Immediately after burning, foot *R* was injected subcutaneously with tissue extract; foot *L* was untreated in any way. It is clear enough that in foot *R*, where the exudate from the capillaries was caused to clot promptly and probably completely by the tissue extract injection, swelling is far more

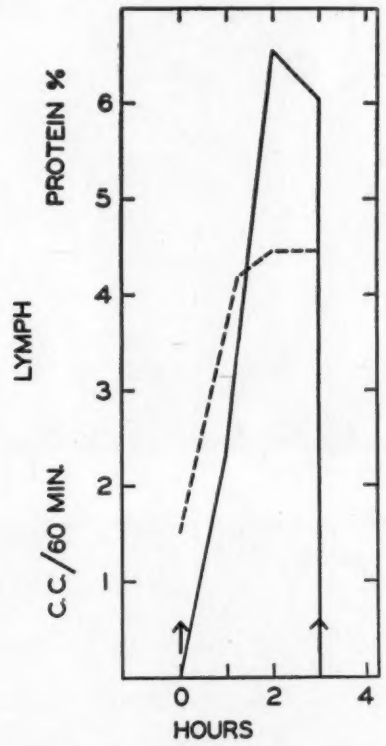

Fig. 2.—Three hours after 2 minutes' immersion of a front foot in water at 100° C., when swelling had become marked and lymph flow rapid, tissue extract was injected subcutaneously into the burned region. Lymph flow ceased instantly and was not resumed during the following 12 hours. Burn at *O*, tissue extract injection at third hour. *Solid line*, lymph flow; *broken line*, percentage of protein in the lymph.

marked than in foot *L*, which was untreated and possessed unobstructed lymphatic drainage. A third pair of photographs (not used in this paper), taken 4 hours and 40 minutes after the burn, show foot *R* almost exactly as in Fig. 3. Foot *L* was more swollen but still behind the right foot, where coagulation of the exudate from the blood capillaries was assured by tissue extract injection.

It is clear that local swelling depends notably upon the degree to which coagulation of the exudate occurs with imprisonment of the water which leaks from the blood capillaries.

Fig. 4 illustrates an experiment in which the normal forefeet of a dog are shown above, and below, a photograph of the right foot 2 hours after 2 minutes' immersion in boiling water. No tissue extract was injected. Lymph flowed profusely from the cannula and clotted normally. At the end of 2 hours and after photographing the right foot, the dog was given a large dose of heparin intravenously so that for the rest of the

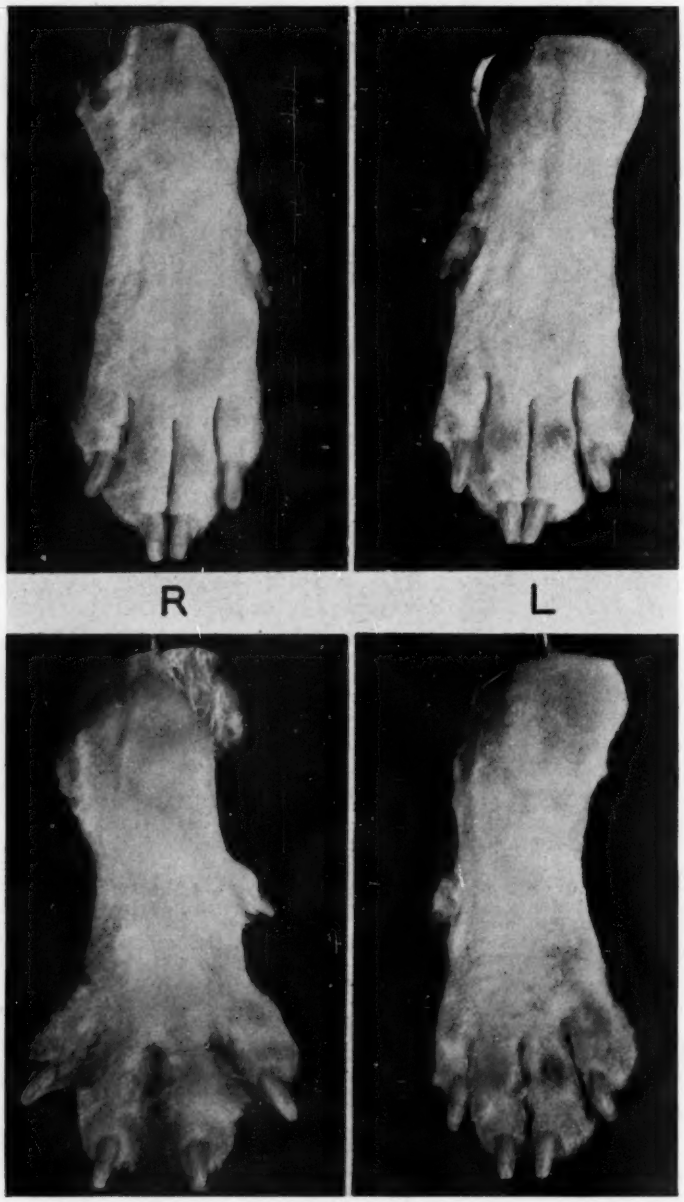

Fig. 3.—The upper pair of front feet are normal prior to simultaneous immersion in water at 100° C. for 2 minutes. In the lower photograph, foot *R* was injected subcutaneously with tissue extract immediately after burning, and foot *L* was allowed to take its normal course. Swelling in the foot *R*, which received tissue extract, is very marked as compared with foot *L*. The lower photograph was made 1 hour and 45 minutes after the burn.

experiment his blood and lymph were incoagulable. Immediately following heparinization the left foot was dipped in boiling water for 2 minutes and photographed as shown in Fig. 4, *L*, lower picture, exactly 2 hours later. Swelling has occurred but it is much less extensive than in the right foot, where a certain degree of coagulation of the exudate has occurred.

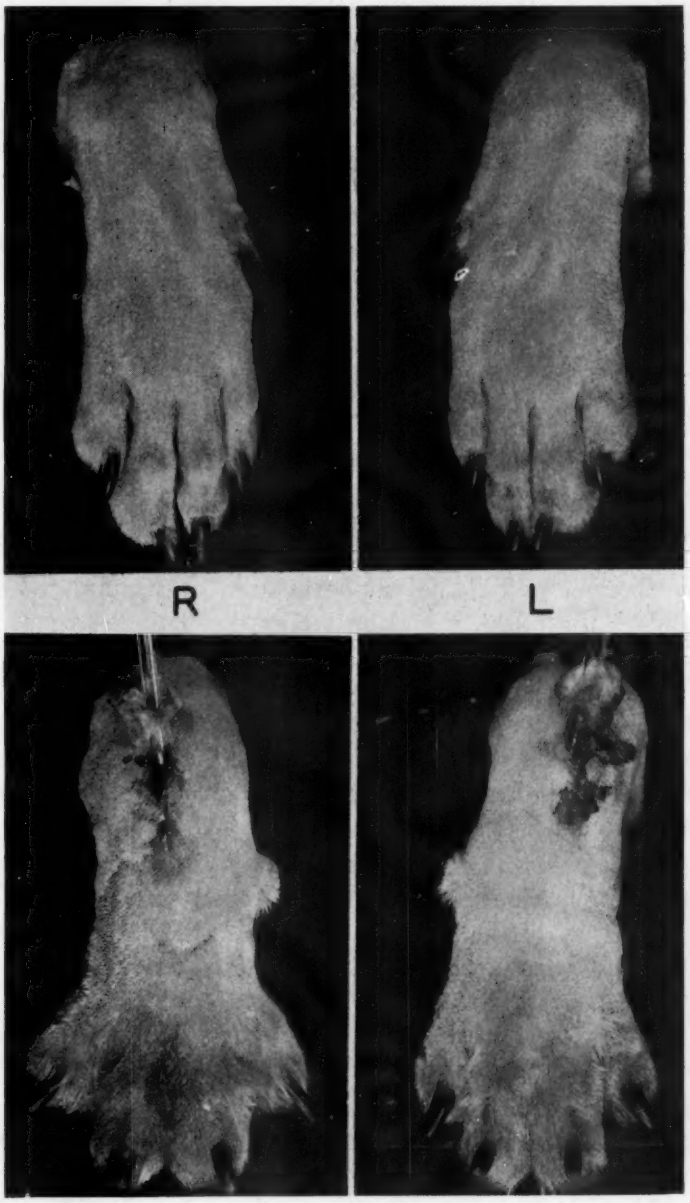

Fig. 4.—The upper pair of front feet are normal. Prior to burning, a lymphatic had been cannulated in each case. The lower photograph of the right foot was taken 2 hours after 2 minutes' immersion in boiling water. The animal was then thoroughly heparinized and the left foot dipped in boiling water for 2 minutes. The lower photograph of the left foot shows much less swelling due to completed prevention of clotting by the heparin.

DISCUSSION

These findings are of practical importance in several ways. First of all, lymphatic drainage can be blocked almost instantly and completely if the region damaged is either supplied with tissue extract artificially, or through the nature of the accident, so crushed and mutilated as to supply tissue extract naturally and thus bring about immediate coagulation of the exudate or blood from the capillaries. There is no doubt that localization of a spreading irritant, such as is faced in the growth of bacteria in an area of infection, may be beneficial. In the case of a burn of great severity, such as that used in these experiments, the heat acts for a given time and then the immediate problem for the animal consists in getting rid of the damage and its consequences. No one who sees the swelling and accumulation of coagulum, which occur locally when a foot is burned, as we have done, can fail to realize that if such an injury is to heal the animal must not only dispose of the tissue killed by the burn but must also get rid of a very large amount of clotted blood which is an unfortunate accessory to the injury. In an uninfected burn local accumulation of exudate, which is promoted greatly by fibrin formation, adds to the problem of healing though at the same time limiting absorption through the lymphatics. This last fact is not so important in connection with burns as we had hoped, since we have been able to show that if all four feet are burned for 2 minutes by immersion in boiling water, and prior to the burn the thoracic and right lymphatic ducts are cannulated so that no lymph enters the blood, the animal may die with the usual syndrome accompanying severe burns, lowered plasma volume, and falling blood pressure. It seems probable that a toxin is absorbed directly into the blood from burned areas and while the same substance is present in the lymph from such regions, blood absorption is so constant and so great as to cause death even though lymphatic participation in the disaster is excluded.

It is an interesting fact that though a severe burn such as has been used in these experiments must kill many cells in the skin and even in the deeper tissues of the foot, the burn does not cause immediate liberation of thromboplastic material in significant amounts, and it is only after 8 to 10 hours that lymph flow begins to slow down indicating, perhaps, that enough cell breakdown has occurred to convert prothrombin to thrombin and bring about extensive coagulation.

Another fact surprising to us consisted in the persistence of circulation through the capillaries of the burned foot, circulation which must be quite extensive. The foot swells rapidly when removed from the boiling water and lymph flows freely from cannulated vessels. These facts mean circulation through hyperpermeable capillaries and this fact is borne out if the animal is given a dye such as T-1824 intravenously. The lymph at once becomes blue and at autopsy the swollen tissues of the

foot are similarly stained. Heat alone, applied to a normally circulated part, does not induce generalized vascular thrombosis. There is, however, in burns so extensive as we have used, a certain amount of local hemolysis reflected within several minutes by pink coloration of the lymph collected from the foot. It is also possible to show that in addition to the direct local effect of heat in causing hemolysis, a hemolytic substance is liberated from the burned tissues which causes hemolysis in the dog and in vitro if lymph is collected and mixed with dog cells.

The experiments described in this paper are designed to establish the necessity for a standard, repetitive method of causing burns; to show that coagulation of the exudate from a burned area is capable of checking lymph flow, if it is complete enough; and to establish a basis for other experiments upon burns, such as the toxic nature of the lymph collected from burned areas, the effects of severe burns on capillary permeability in sound parts of the body, and the effect of confining the burned part in plaster of Paris immediately after removal from the boiling water and before swelling begins. Experiments in all these directions have been carried out and reports upon them will be issued as rapidly as possible.

SUMMARY

A simple method for making a standard burn by immersion of the foot of an anesthetized dog in boiling water is described.

The effects of coagulation of the exudate caused by the burn are described.

The failure to prevent collapse and death by blocking lymph flow is mentioned and will be discussed further in future papers.

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EXPERIMENTAL PULMONARY EDEMA FOLLOWING LOBECTOMY AND PLASMA INFUSION

JOHN H. GIBBON, JR., M.D., AND MARY H. GIBBON, PHILADELPHIA, PA.
(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania)

IN A previous article[4] it was demonstrated experimentally that when there has been an acute reduction in pulmonary tissue, a blood transfusion of a size well tolerated by normal animals may produce pulmonary edema, decreased saturation of the arterial blood with oxygen, and death. We also reported the histories of two patients who died some hours after the completion of bilateral lobectomies. Both patients received not only blood transfusions, but also rather large plasma infusions. In the two clinical cases reported it is conceivable that the infusion of plasma may have contributed to the pulmonary edema from which the patients died.

That pulmonary edema may occur during the course of a plasma infusion, when the heart is damaged and a tendency toward pulmonary vascular congestion is present, is illustrated by the following report.

CASE REPORT.—J. I., a 71-year-old white woman, entered the hospital complaining of marked shortness of breath. She had the signs and symptoms of congestive heart failure: an enlarged, tender liver and râles at the bases of both lungs. There was also a palpable enlargement of the thyroid gland. The basal metabolic rate was 53 per cent above normal. With rest in bed and digitalis the signs of congestive failure disappeared with the exception of the persistence of râles at the bases of both lungs. The basal metabolic rate fell to plus 40 and remained at that level.

After ten days of iodine medication a subtotal thyroidectomy was performed under local anesthesia. Following the operation the patient had several attacks of dyspnea associated with congestion at the bases of the lungs and signs of consolidation in the right lower lobe. X-ray confirmed the clinical diagnosis of bronchopneumonia of the right lower lobe. There was little febrile reaction, however, and under sulfathiazole and oxygen therapy the signs of pneumonia cleared up in three or four days, and thereafter her convalescence was relatively uneventful. On the eighth postoperative day she was given a plasma infusion because of a low plasma protein concentration. The infusion was given slowly but had to be discontinued after the administration of 300 c.c., because of marked dyspnea associated with loud moist râles throughout both lung fields.

A similar episode occurred on the tenth postoperative day. A plasma infusion was again administered cautiously but had to be discontinued because of the same symptoms of pulmonary edema as had appeared before. An hour or so after terminating the plasma infusion, the signs of pulmonary edema had completely disappeared and the patient was comfortable. On the evening of the same day the patient complained of pain in her chest, developed symptoms of shock, and died suddenly, presumably from a coronary thrombosis. Permission for autopsy was not granted.

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Thus, in a patient in whom there was a tendency toward pulmonary edema from left heart failure, the intravenous administration of plasma on two occasions produced the signs and symptoms of acute pulmonary edema.

The following experiments are concerned with the effects of plasma infusions in animals in which the functioning pulmonary tissue has been acutely reduced. As in our earlier work, the experiments are divided into three groups. In the first group, a plasma infusion of 15 c.c. per kilogram of body weight was administered over a period of thirty minutes to normal cats. In the second group, approximately 71 per cent of the pulmonary tissue was surgically removed and the cats were observed for several hours afterward. In the third group of animals the same amount of pulmonary tissue was removed as in Group 2, and this procedure was followed by plasma infusions similar to those given the cats in Group 1.

METHOD

Cats were anesthetized by an intraperitoneal injection of a 5 per cent solution of sodium amytal (50 mg. per kilogram of body weight). A large glass cannula was tied into the opened trachea in the neck to ensure a free passage of air. The right femoral vessels were exposed and arterial blood samples were withdrawn from the femoral artery into an oiled syringe at the start of each experiment and at appropriate intervals thereafter. One cubic centimeter of this blood was placed in a small test tube containing 0.1 c.c. of solution of ammonium oxalate (1.2 per cent) and potassium oxalate (0.8 per cent) to prevent coagulation. The blood was allowed to stand for one-half hour in a Wintrobe hematocrit tube and was then centrifuged at 2000 r.p.m. for thirty minutes. The percentage of red cells was noted, the supernatant plasma was drawn off and the plasma protein concentration determined by the method of Barbour and Hamilton[1] as modified by Drew, Scudder, and Papps.[3] The remainder of the blood in some experiments was transferred to an oxalated tube under oil and surrounded by ice. In these experiments carbon dioxide and oxygen content and oxygen capacity of the blood were determined by the Van Slyke manometric method.

Every sample of blood that was withdrawn was replaced with an equal quantity of blood obtained from another cat and injected into the femoral vein. The blood used for the replacement of samples was obtained under sterile conditions and kept in a sterile flask in the icebox until used. The blood was never more than seven days old. The plasma used for the infusions was obtained by bleeding a cat to death under sterile precautions. The blood was collected in sterile 50 c.c. tubes and centrifuged at 2000 r.p.m. for twenty minutes. The plasma was aspirated and stored in sterile flasks at 5° C. until used. Cultures of the plasma were not made before use in experiments, but any plasma showing a trace of hemolysis or cloudiness was discarded.

The control plasma infusions in Group 1 were in the majority of experiments made with the same lot of plasma which had been used in the experiments in Group 3. Thus, an experiment of the Group 3 type, with lobectomy followed by a plasma infusion, was followed the next day by a control experiment in which the same plasma was infused into a normal cat. The plasma infusions consisted of 15 c.c. plasma per kilogram of body weight, given over a period of thirty minutes in both the control Group 1 and the lobectomized animals, Group 3. The plasma was administered through a burette connected by rubber tubing to a glass cannula tied in the femoral vein.

In cats the right middle and all the lower lobes of the lungs comprise approximately 71 per cent of the pulmonary tissue. This figure was derived by determining the proportion of the weights of these lobes to the total lung weight in twenty-six normal cats. The figures varied between 66 and 75 per cent, averaging 71 per cent. The removal of the right middle and all the lower lobes was performed in Groups 2 and 3 by the same technique as previously employed.[4] A No. 12 French catheter with an open end was threaded into the glass tracheal cannula until its tip lay within the trachea. While the pleural cavities were open, artificial respiration was administered by the intermittent insufflation of air through this catheter. Lobectomies were performed through an incision in the sixth intercostal space on either side. After division of the pulmonary ligaments, the hilar structures of the lobes to be removed were tied with a single ligature of heavy silk and the lobes were then resected. A small rubber tube with several perforations near the tip was introduced into each pleural cavity through a stab wound in the eighth intercostal space. The incision in the sixth interspace was then closed with a continuous suture, approximating the sixth and seventh ribs. The overlying muscles and skin were similarly sutured. At the conclusion of the bilateral operation, which required approximately twenty-five minutes to perform, the catheters draining the pleural cavities were connected to a constant source of 7 cm. water suction. A T tube inserted into the suction line was connected with a glass U-shaped water manometer in order to read respiratory variations in intrapleural pressure. After the chest was closed and suction established, artificial respiration was discontinued and the small rubber catheter withdrawn from the trachea. The lobes of the lungs removed at operation were kept in closed containers until their weights were determined.

At the conclusion of the experiment an autopsy was performed. Surviving animals were sacrificed by bleeding. The trachea was then clamped and the thoracic cavity widely opened by removing the sternum and the costal cartilages. Any fluid in the pleural cavities was noted and the amount measured. The color and condition of the lungs, or remaining lobes were noted. The lobes were resected separately by

dividing the vessels and bronchi of each lobe close to the pulmonary tissue. The presence or absence of froth in the trachea or bronchi was noted. The heart was removed from the pericardium, all the great vessels being divided close to the base of the heart. The resected pulmonary lobes and the heart were then weighed to an accuracy of 10 mg.

RESULTS

In general, the results were similar to those previously reported with blood transfusion.[4] The mortality in the three groups of experiments is shown in Table I. The plasma infusion in normal cats produced no noticeable effects and none of the animals died, Table I, Group 1. Following the completion of the infusion, the animals were observed for periods of time varying from 3 hours and 30 minutes to 5 hours and 20 minutes, with two exceptions in which the animals were sacrificed 28 minutes and 2 hours and 20 minutes after the infusion. All these cats, without exception, were in good condition at the time of sacrifice.

In fifteen cats the right middle and all the lower lobes were resected as described above. Three cats in this group died, Table I, Group 2. Two of these had gross evidence of pulmonary edema: progressive cyanosis, coarse râles in the trachea, and froth exuding from the tracheal cannula. They died 1 hour and 5 minutes, and 1 hour and 10 minutes after completion of the lobectomy. The third animal died suddenly of cardiac arrest, presumably from ventricular fibrillation, 37 minutes after lobectomy during the injection of 10 c.c. of blood into the femoral vein to replace a blood sample which had been withdrawn a short time

TABLE I

MORTALITY FOLLOWING (1) PLASMA INFUSION IN NORMAL CATS, (2) REMOVAL OF ALL LOWER LOBES AND RIGHT MIDDLE LOBE AND (3) REMOVAL OF ALL LOWER AND RIGHT MIDDLE LOBES FOLLOWED BY PLASMA INFUSION

GROUP	TYPE OF EXPERIMENT	NUMBER OF ANIMALS	MORTALITY	
			NUMBER	PER CENT
1	Plasma infusion in normal cats	9	0	0
2	Resection of 71% of pulmonary tissue	15	3	20
3	Resection of 71% of pulmonary tissue followed by plasma infusion	11	8	73

before. This was the only instance in the thirty-five experiments reported here in which this accident occurred. The other twelve animals were observed for from 3 to 6 hours after the lobectomies and then sacrificed, with one exception when the animal was sacrificed 2 hours and 13 minutes after the lobectomy. None of these twelve cats were cyanotic, no tracheal râles were heard, and there was no fluid in the trachea at the time of sacrifice.

In eleven cats the right middle and all the lower lobes were removed as in Group 2. From 25 minutes to 1 hour and 49 minutes after the completion of the lobectomies, the plasma infusion was started. Eight of the eleven cats died at intervals of time varying from 50 minutes to 2 hours and 15 minutes after the completion of the infusion, Table I, Group 3. Before death all these animals exhibited signs of pulmonary edema: râles in the trachea, marked cyanosis, and in most instances froth bubbling in the tracheal cannula. In three experiments the cats appeared to be unaffected by the plasma infusion. They were sacrificed at 2 hours and 5 minutes, 2 hours and 55 minutes, and 3 hours and 30 minutes after the completion of the plasma infusion, at which time there was no cyanosis, no tracheal râles could be heard, and there was no froth in the tracheal cannula. Thus, as can be seen in Table I, plasma infusion in normal cats carries no mortality, the resection of approximately 71 per cent of pulmonary tissue has a 20 per cent mortality, while the resection of 71 per cent of pulmonary tissue followed by a plasma infusion has a 73 per cent mortality.

The evidence for the presence of pulmonary edema in Groups 2 and 3 was the manner of death, with progressive cyanosis, labored respiration and froth in the trachea, and the autopsy findings. In all the animals that died from pulmonary edema, froth was present in the trachea and exuded from the main stem bronchi when cut. In Table II the weights

TABLE II

WEIGHT OF RIGHT UPPER AND LEFT UPPER AND MIDDLE LOBES EXPRESSED AS PER CENT OF WEIGHT OF BODY AND OF HEART IN FOUR GROUPS OF CATS*

GROUP	TYPE OF EXPERIMENT	PER CENT WEIGHT OF BODY		PER CENT WEIGHT OF HEART	
		VARIATION	AVERAGE	VARIATION	AVERAGE
	26 normal cats	.12 to .22	.16	33 to 57†	44†
1	9 normal cats with plasma infusion	.17 to .24	.20	43 to 60	51
2	Removal of right middle and all lower lobes in 13 cats	.20 to .35	.26	54 to 89	70
3	Removal of right middle and all lower lobes followed by plasma infusion in 8 cats	.43 to .91	.56	99 to 184	139

*In normal cats, in normal cats with plasma infusion, in cats from which the right middle and all lower lobes had been removed, and in cats with the same amount of pulmonary tissue removed, followed by a plasma infusion.

†Figures obtained in seven normal cats.

of the right upper and left upper and middle lobes, that is, the remaining lobes when lobectomy was performed, are expressed in relation to the weight of the body and of the heart in Groups 1, 2, and 3, and in normal cats. These lobes in normal cats given plasma infusions were slightly heavier than in normal cats without plasma infusion. In the thirteen cats in Group 2 which did not develop pulmonary edema, there was an increase in the weight of the remaining lobes of approximately 60 per cent. This increase in weight was probably due to congestion

of the vascular bed of these pulmonary lobes, as there was no gross evidence of fluid in the bronchi. The weights of the remaining lobes of the two cats in Group 2 which died with evidence of pulmonary edema fell within the range of the weights of the corresponding lobes of the eight animals in Group 3 which also died of pulmonary edema. Expressed as per cent of body weight they were 0.50 and 0.55; expressed as per cent of heart weight they were 114 and 144. The cat in Group 2 that died suddenly during the injection of blood had no evidence of pulmonary edema during life or at autopsy, and is included among the thirteen cats in Group 2 which were sacrificed and did not have pulmonary edema. The weight of the remaining lobes in this animal was 0.28 per cent of the body weight and 70 per cent of the heart weight.

The weights of the remaining lobes of the eight cats in Group 3 which died from pulmonary edema averaged more than three times the weight of the corresponding lobes in normal cats. They were grossly congested and edematous and froth poured from the openings of the cut bronchi. In the three cats in Group 3 which lived until sacrifice without evidence of pulmonary edema, the remaining lobes weighed approximately the same as those in the cats which had no pulmonary edema in Group 2. Expressed in per cent of body weight they were 0.22, 0.30, and 0.26; expressed in per cent of weight of heart they were 0.64, 0.69, and 0.80.

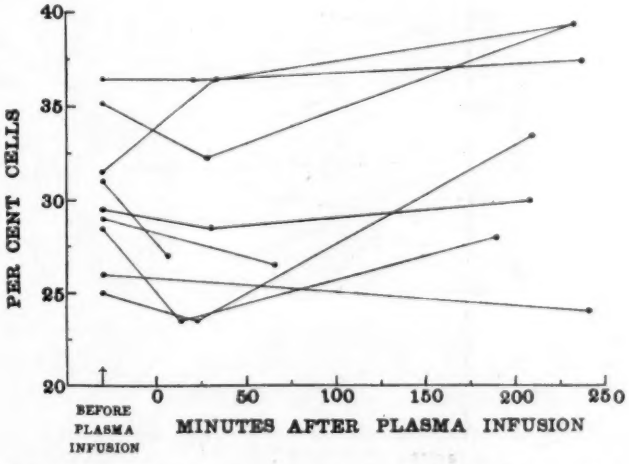

Fig. 1.—Hematocrit values in normal cats before and after plasma infusion.

The changes in hematrocit values and plasma protein concentrations are graphically shown in Figs. 1 to 6, inclusive. As can be seen, there are no consistent changes in these values except in Figs. 2 and 4. In Fig. 2 the hematrocit values before and after removal of 71 per cent of pulmonary tissue are shown. There is a definite tendency for the percentage of cells in the circulating blood to increase after the acute reduction in the pulmonary vascular bed. The explanation for this increase is not as yet clear. It is apparent that plasma was lost from the circulating blood, and one would expect this loss to occur through

the capillary and alveolar walls of the remaining pulmonary lobes because of the existing congestion. However, only two of the animals in this group developed pulmonary edema in amounts sufficient to be

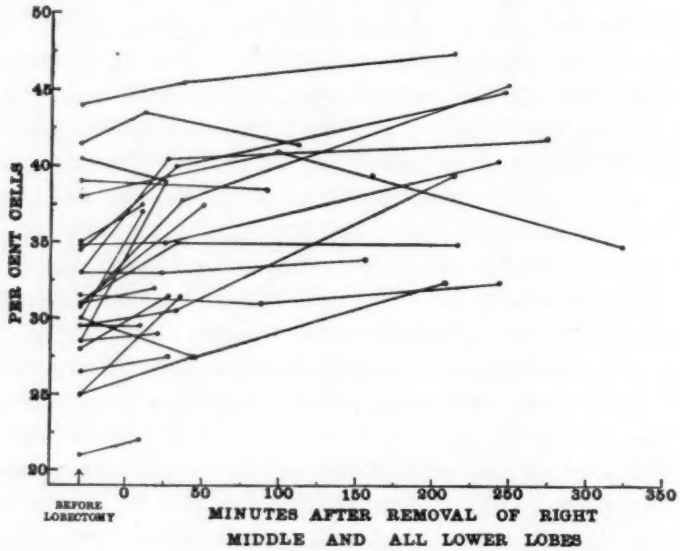

Fig. 2.—Hematocrit values before and after removal of the right middle and all lower lobes.

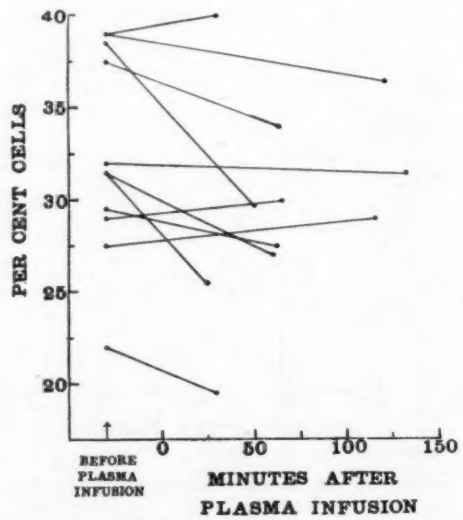

Fig. 3.—Hematocrit values before and after plasma infusion in lobectomized cats.

noticed grossly and to cause death. A similar hemoconcentration following extensive removal of pulmonary tissue was noted in the experiments previously reported.

In Fig. 4 there is shown a consistent increase in the plasma protein concentration in normal cats following a standard plasma infusion. The plasma protein concentration in animals of Group 2, as shown in

Fig. 5, shows variable changes which are too irregular to be significant. However, in Fig. 6 it can be seen that in only three experiments was there a significant rise in the plasma protein concentration following

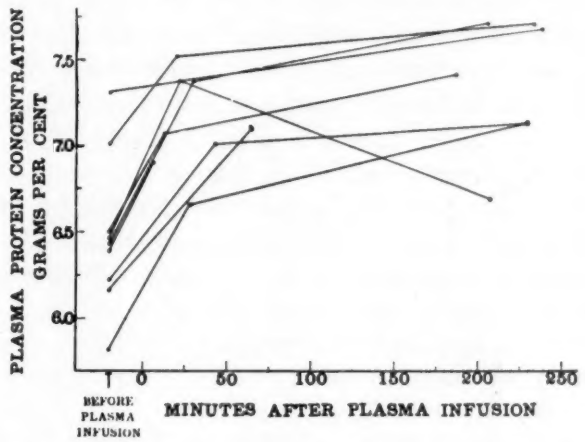

Fig. 4.—Plasma protein concentration in normal cats before and after plasma infusion.

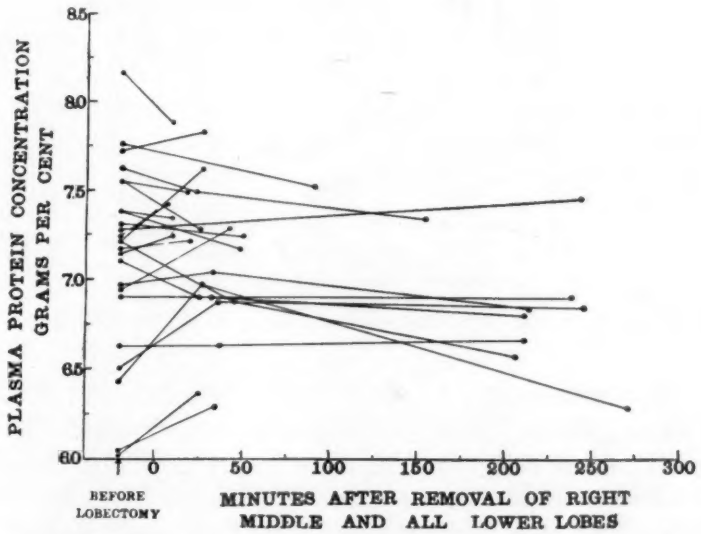

Fig. 5.—Plasma protein concentration before and after removal of the right middle and all lower lobes.

a plasma infusion in lobectomized cats. In the remaining eight experiments there was practically no change in concentration. When these results are compared with those shown in Fig. 4, it is apparent that protein was lost from the blood stream by the animals in Group 3. The pulmonary edema which followed the infusions of plasma undoubtedly represents some of this lost plasma.

The concentration of the protein in the plasma used for the infusions varied between 5.7 and 6.6 Gm. per cent, averaging 6.2 Gm. per cent, with one exception. In this instance the plasma used had a concentra-

tion of only 4.8 Gm. per cent, and this plasma was used for infusion in one of the three animals in Group 3 which survived the infusion following a lobectomy. This fact, however, is probably without significance, as the other two animals which survived in Group 3 were infused with plasma having a protein concentration of 6.0 and 6.6 Gm. per cent. In six instances fluid was obtained from the tracheae of animals dying with pulmonary edema for determinations of the protein concentration, which varied between 5.2 and 6.2 Gm. per cent, and averaged 5.7 Gm. per cent. The plasma protein concentration of the blood of thirty-three normal cats varied between 5.8 and 8.2 Gm. per cent, averaging 7.0 Gm. per cent. Thus it is evident that the fluid which filled the bronchi and tracheae of the animals dying from pulmonary edema consisted of only slightly diluted plasma.

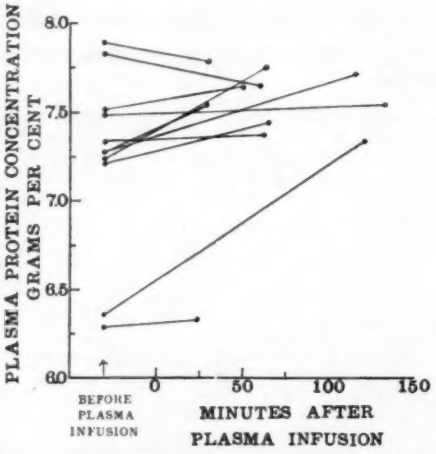

Fig. 6.—Plasma protein concentration before and after plasma infusion in lobectomized cats.

A few determinations were made of the saturation of the arterial blood with oxygen in the three groups of experiments. The results were entirely similar to those reported previously with blood transfusions following lobectomy. In Group 1, the saturation of the arterial blood with oxygen was determined in three instances following plasma infusions in normal cats. In each instance the blood was found to be adequately saturated with oxygen, the figures being 96, 93, and 95 per cent. In Group 2 the saturation of the arterial blood with oxygen was determined in six instances at time intervals after the completion of the lobectomy varying from 1 hour and 51 minutes, to 5 hours and 22 minutes. In each instance the blood was adequately saturated with oxygen, the values being 92, 92, 94, 93, 95, and 100 per cent saturation. In the two animals that died from pulmonary edema, the oxygen saturation was not determined. In the animal that died suddenly during the injection of blood, the arterial blood was 99 per cent saturated with oxygen 10 minutes before death. In Group 3, the saturation of arterial

blood with oxygen was determined in four experiments following the plasma infusion. In three of these experiments the animals died 21, 20, and 32 minutes after the blood sample was taken for analysis. The saturation of the arterial blood with oxygen was respectively 66, 58, and 73. In the fourth experiment the animal survived the plasma infusion and the arterial blood was 94 per cent saturated with oxygen 2 hours and 12 minutes after the completion of the infusion.

DISCUSSION

Edema occurs because of increased capillary blood pressure, decreased colloid osmotic pressure of the blood plasma, or because of increased permeability of the capillary endothelium. It is the first of these causes which we believe operates in the pulmonary edema consequent upon blood or plasma infusions following acute reduction of the pulmonary vascular bed. After removal of 71 per cent of pulmonary tissue, the entire output of the right heart must pass through the remaining 29 per cent of the pulmonary vascular bed. If the cardiac output is not diminished, the increase in blood flow through the left upper and middle and right upper lobes would amount approximately to 345 per cent. That there is no gross diminution of the cardiac output is evidenced by the fact that the systemic arterial and venous blood pressures are within normal limits following lobectomies.[4] With exercise the blood flow through normal human lungs may be increased from 600 to 800 per cent[2] without the production of pulmonary edema, although under these circumstances there is an increased volume of blood in the lungs. In the experiments reported here the increase in weight of the remaining lobes following removal of 71 per cent of pulmonary tissue might be due to an increased volume of blood in the pulmonary vascular bed.

In conclusion, the frequent and ever-increasing use of plasma and blood transfusions in all fields of surgery justifies a word of caution as regards their indiscriminate use in thoracic surgery. When there has been any impairment of cardiorespiratory function, following or during a thoracic operation, it seems to be advisable to employ intravenous fluids which tend to remain in the blood stream, such as blood and plasma, with a certain degree of caution, and to be on the lookout for developing signs of pulmonary edema.

SUMMARY

1. A plasma infusion of 15 c.c. per kilogram of body weight was given at a constant rate over a period of thirty minutes to nine normal cats. There were no signs of pulmonary edema before sacrifice or at autopsy.

2. The right middle and all the lower lobes of the lungs were removed from fifteen cats. Two of these animals died from pulmonary edema and there was one accidental death. The other twelve were sacrificed

between 4 and 6 hours after the operation. None of these animals showed evidence of pulmonary edema before death or at autopsy.

3. In eleven animals after removing the same lobes of the lungs, a plasma infusion of 15 c.c. per kilogram of body weight was given over a period of 30 minutes. Three of these animals lived and were sacrificed between 2 and 4 hours later. There was no evidence of pulmonary edema before death or at autopsy. The remaining eight animals died from 1 to 2 hours after completion of the infusion with clinical evidence of pulmonary edema and gross evidence at autopsy of fluid filling the tracheae and bronchi.

4. The hematocrit values showed no constant change before and after plasma infusions in the normal and in lobectomized cats. There was generally a definite increase in the hematocrit values following the acute removal of 71 per cent of pulmonary tissue.

5. The plasma protein concentration was consistently elevated following plasma infusions in normal cats. There was a variable change in plasma protein concentration before and after lobectomy and after plasma infusion in the group of lobectomized cats.

6. The saturation of the arterial blood with oxygen was determined in a few experiments. The arterial blood was adequately saturated with oxygen in all the normal and lobectomized animals which did not die from pulmonary edema. In the animals dying from pulmonary edema, saturation of the arterial blood with oxygen was decreased.

7. There was no significant increase in the weights of the lungs of normal cats following plasma infusion. Following removal of the right middle and all the lower lobes in the animals that did not develop pulmonary edema, the remaining lobes showed an increase in weight of approximately 60 per cent. After removal of the lobes mentioned, followed by a plasma infusion, the animals that died showed an increase in the weight of the remaining lobes of approximately 300 per cent.

CONCLUSION

In cats, when there has been an acute reduction of pulmonary tissue, a plasma infusion of a size well tolerated by normal animals may produce death from pulmonary edema.

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THE RENAL RESPONSE TO HYPERTONIC SUCROSE SOLUTIONS*

G. FEHER, M.D., S. RODBARD,† PH.D., AND L. N. KATZ, M.D.
CHICAGO, ILL.
(From the Cardiovascular Department, Michael Reese Hospital, Chicago)

INTRAVENOUS hypertonic sucrose has been widely used in the clinic for a variety of purposes without apparent ill effect. Recently, however, the question has been raised as to whether such indiscriminate use is justified since it has been reported to lead to impairment of kidney function and to histologic evidence of tubular damage.[1-7] Further, the changes found in the renal tubular epithelium might possibly affect the mechanism of nephrogenic hypertension. It is also conceivable that the increased load on the kidney resulting from the retention of waste products which sucrose injections cause, could result in an aggravation of the hypertension. These considerations led us to reinvestigate the action of hypertonic sucrose on normotensive and hypertensive dogs with and without pre-existing renal excretory insufficiency.

LITERATURE

The most extensive clinical use of sucrose is its employment in the reduction of intracranial pressure.[8-12] Intravenous hypertonic sucrose lowers intracranial pressure without the secondary rise seen with the use of hypertonic dextrose.[8] Other uses for sucrose have been recently suggested, also based for the most part on a similar tissue dehydrating action. It has been utilized preoperatively in glaucoma,[13] in the treatment of chronic hypertension,[10] as a diuretic agent in nephrosis[14] and in other conditions,[15] in chronic alcoholism,[16] as well as in bronchial asthma in conjunction with adrenalin.[17] It has been utilized to measure glomerular clearance[18] and extracellular fluid.[19]

The cardiovascular response to the hypertonic sucrose solution is a transient hypervolemia with attendant increases in venous pressure, heart rate, cardiac minute output, and arterial blood pressure.[20] These effects are transitory. Almost all the sucrose is excreted within the first few hours.[18]

It has been clearly demonstrated in dogs,[1, 3] in rabbits,[2] and in man,[2, 4-7] that intravenous injections of hypertonic sucrose in large amounts lead within an hour to swelling of the convoluted tubules of the kidney, associated with a fine vacuolar degeneration, nuclear shrinkage, and the presence of granular exudate in the glomerular lumen. These changes reach a maximum on the third day and then gradually subside. With repetition of the injections every third day or oftener, the renal changes are found to be more severe and the phenolsulfonphthalein clearance is markedly lowered.[2] Even after several sucrose injections the function and appearance of the renal epithelium show a remarkable ability to return to normal[2, 3] but a prolonged series of injections tends to produce sclerosis and atrophy of the kidney with a reduction in renal excretory function.[2, 3] Dextrose,[3] sorbitol,[3] and inulin[21] apparently do not lead to such lesions.

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†Eli Lilly Fellow.
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METHOD

Hypertonic solutions were prepared by dissolving 50 Gm. of sucrose* in distilled water and diluting to 100 c.c. Blood pressures were determined with the Hamilton manometer[22] on trained unanesthetized dogs according to the technique used in this laboratory.[23] Hypertension was induced by the technique of Goldblatt,[24] and relative renal excretory insufficiency was either an associated circumstance in such animals or was induced by temporarily completely occluding the renal arteries for one hour.[25] Renal excretory impairment was evaluated by determining blood N.P.N.† and by comparing the specific gravity of the urine after dehydrating the animals for twenty-four hours during which time only dry food was permitted.

RESULTS

1. *Unoperated Normotensive Dogs Without Preliminary Evidence of Renal Excretory Insufficiency.*—Seven dogs received 200 c.c. of 50 per cent sucrose daily for five, six, six, nine, ten, ten, and thirteen consecutive days, respectively. In three of these animals a rise in blood N.P.N. to about 60 mg. per cent was evident on the third day of injections, but the N.P.N. returned to normal after three more days. The other four dogs showed no change in N.P.N. Before the series of injections the animals were able, after twenty-four hours without water, to concentrate the urine to a specific gravity of 1.050. Two days after the injections were completed the kidneys could concentrate only to about 1.025. However, a week later the control-concentrating ability was usually regained. The urine remained clear and free of albumin and casts. The blood pressure of all seven dogs remained unchanged during and after the injection period.

2. *Normotensive and Hypertensive Dogs With Preliminary Evidence of Reduced Renal Excretory Reserve.*—Two normotensive and three hypertensive dogs with reduced renal excretory reserve, due to partial occlusion of the renal arteries, were used in this series. Each dog received a total of 500 c.c. of 50 per cent sucrose administered in 100 c.c. doses every third day. No effect was observed on the blood N.P.N. level, but the renal concentrating power was definitely reduced in each case as in the preceding series. These animals then received daily injections of 100 c.c. of 50 per cent sucrose over eight days. During this period all showed a transient rise in blood N.P.N. with the appearance in the urine of formed elements and albumin, red and white blood cells. The ability of the kidney to concentrate urine remained at a low level, but rose to normal values a week after the cessation of injection.

After four weeks, all five dogs received daily injections of 200 c.c. of 50 per cent sucrose for seven, ten, twelve, thirteen, and sixteen days respectively. This procedure led to a rise in blood N.P.N., pulmonary edema, azotemia, and death in two animals. In the other three dogs a

*We are grateful to Dr. M. Gordon of Endo Products for supplying us with the ampoules of 50 per cent sucrose.

†We are indebted to Dr. D. J. Cohn, Head of the Department of Biochemistry, for these determinations.

transient azotemia occurred. After an interval of a week, two dogs received another series of daily injections of 200 c.c. of sucrose for ten and thirteen days, respectively. This was accompanied by a transient rise in blood N.P.N. which returned to the normal level before the injections were ended. No significant changes in blood pressure were noted in this series.

3. *Tolerance to Sucrose.*—The recovery from the renal damage following the sucrose injections despite continuation of the injections suggested that a more adequate tolerance might be established by the use of graded doses. This possibility was tested in fifteen dogs, six normal and nine with hypertension and reduced renal reserve. These dogs were given daily sucrose injections beginning with 10 c.c. on the first day and with the amount injected increased by 20 c.c. each day, until 200 c.c. was reached; this was followed by six injections of 200 c.c. in the next six days. No evidence of renal impairment was noted either in the blood N.P.N. or in the ability to concentrate the urine on dehydration two days after the end of the injections. No alterations in blood pressure were observed.

Four other animals with reduced renal excretory reserve and hypertension were given daily injections of 10 c.c. of sucrose for four days, followed by daily injections of 200 c.c. of sucrose for four days. A transient increase in blood N.P.N. and a marked reduction in the ability to concentrate urine were observed. The blood N.P.N. quickly returned to the previous level, and after ten to twenty-five days the kidneys had almost completely regained their previous function and concentrating ability.

4. *Deaths Occurring During the Experiments.*—Eight of the animals receiving sucrose died during the period of injections, six during a period of hot weather. Death occurred from six to twenty-seven days after the injections were begun. In all, death was associated with pulmonary involvement; six died of pneumonia, and the other two dogs died with pulmonary edema and azotemia.

DISCUSSION

The injection of hypertonic sucrose has been reported to lead to anatomic changes particularly in the tubules.[1-7] It is clear that for a few days, at least, the renal excretory reserve is reduced. In animals in which an initial large amount of renal reserve was present, no demonstrable effects were noted in the blood N.P.N. level nor did protein or other abnormal formed elements appear in the urine. However, the ability of the kidney to concentrate urine was reduced, reflecting the renal tubular alterations. The absence of blood N.P.N. elevation may be due to the polyuria induced by the sucrose, which may become sufficiently large to clear the blood of nonprotein nitrogenous products

even when the excretory ability of the kidneys is reduced. On the other hand, in animals with pre-existing reduced excretory capacity the introduction of the hypertonic sucrose may lead to a transient relative renal excretory insufficiency as evidenced by a rise in blood N.P.N. as well as by a notable reduction in ability to concentrate urine.

The recovery of the ability of the kidney to cope with the systemic excretory needs even while the sucrose injections were being continued suggests that the kidney can in some way compensate for the new conditions. The mechanism of this adjustment is at present not understood. It is significant, however, that gradually increasing dosages of sucrose may avoid even the temporary renal excretory insufficiency. This compensatory mechanism apparently requires gradual rather than abrupt increase in the sucrose doses. Further, the compensation to sucrose injections is quickly lost since, after a short period of rest, a new series of injections will again lead to transient renal excretory insufficiency.

The absence of blood pressure changes in either normotensive or hypertensive dogs is evidence that the changes induced in the renal parenchyma by the hypertonic sucrose do not initiate or inhibit the hypertensive mechanism. During the period of relative retention of excretory products the absence of a rise in the blood pressure once again suggests that the renal factors responsible for the initiation of hypertension and those having to do with the failure of the kidney to excrete waste products are discrete.[27] The mechanism involved in nephrogenic hypertension is, thus, not dependent on the disordered state of tubular metabolism seen in our animals but probably occurs in some other region of the renal apparatus.

Since the tissues of man contain no invertase,[26] injected sucrose may become available for use by pathogenic organisms and may possibly lead to increased virulence of infections, particularly in dehydrated states, which are aggravated by the injection of hypertonic sucrose.

In our experiments extreme conditions were induced by the injection of large amounts of hypertonic sucrose. This was done to determine, if possible, the maximal ability of the normal and abnormal renal apparatus to adjust to these conditions. Except for the preliminary damage brought on by the hypertonic sucrose, little permanent damage was done. It has also been shown that the cardiac minute output is greatly increased after hypertonic sucrose as a result of an increased plasma volume and venous pressure.[28] Evidently a strain is placed upon the heart as well as upon the kidneys. However, it would appear that in the absence of myocardial and renal damage, injections of moderate amounts of hypertonic sucrose are not contraindicated. This agrees with the clinical experience that no deaths have been attributed directly to hypertonic sucrose injections, during the long history of its use for various purposes.

SUMMARY

1. Large amounts of hypertonic sucrose given intravenously to normal dogs led to a transient reduction in the ability of the kidney to concentrate urine, without elevation in blood N.P.N.

2. In dogs with reduced renal excretory reserve treated as above, the reduction in concentrating capacity was associated with a transient rise of blood N.P.N. Adjustment to the daily injections was indicated by the return of the N.P.N. to normal even though the injections were continued.

3. A relative tolerance to sucrose was demonstrated by the use of gradually increasing daily injections.

4. Blood pressure remained unchanged in both normotensive and hypertensive dogs, with and without previous renal involvement.

5. The use of hypertonic sucrose requires caution in cases with renal or myocardial involvement, in general infections or in dehydrated states.

ADDENDUM

Since this paper was written, Rigdon and Cardwell[29] reported nine more cases with anatomic renal involvement following hypertonic sucrose. They found that the renal response depended in part upon the state of dehydration of the patient.

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ANEURYSM OF THE TEMPORAL ARTERY

A Spontaneous Case Cured by Operation

Roswell K. Brown, M.D., and Robert H. Mehnert, M.D.
Buffalo, N. Y.

(From the service of Dr. James H. Lewis, Moses Taylor Hospital, Lackawanna, New York)

THE history of treatment of peripheral aneurysms dates back to antiquity. In the third century Antillus used double ligature incision, and packing. In the fourth century Philagrius advocated excision. In the eighteenth century Hunter demonstrated the value, in certain cases, of ligation at a distance, proximal to arterial branches. The advisability of this procedure obviously depends upon the regional anatomy and the degree of enlargement of the anastomotic channels. The danger of circulatory deficiency and gangrene, which is of paramount importance in the management of many peripheral aneurysms, is of no significance in the temporal region because of the rich anastomoses of the branches of the external carotid artery. In 1884 and 1885, De Santi made a special study of temporal aneurysms and reviewed thirty-seven cases, three or which were considered spontaneous true aneurysms. His record of Thomas Bartholin's case, which was recorded in 1740, is an interesting example of the traumatic type. The following is a translation of De Santi's account.

The oldest observation of aneurysm of the temporal artery is that of Thomas Bartholin. He was called to a child of seven years, whose mother had struck him a violent blow with a stick on the left side of his head.

"It produced instantly," he said, "a pulsatile tumor about the size of a tangerine, blackish, disappearing upon pressure, which in eight days enlarged finally to cover half of the head, i.e., the temple and the forehead from the sagittal suture to the eye. The consulted doctors, being convinced that a dangerous remedy was preferable to certain death, and having obtained the consent of the mother, opened the tumor with a bistouri. It made a notable hemorrhage, but the blood which spurted was arrested by astringents and after some days this child recovered by the grace of God and was returned to his sorrowful mother."

An excellent comprehensive review of the subject of temporal aneurysm was published by Winslow and Edwards in 1934 and 1935. They tabulated the important data on cases from the literature: 9 spontaneous, 79 traumatic, 5 unclassified, 15 arteriovenous, and 10

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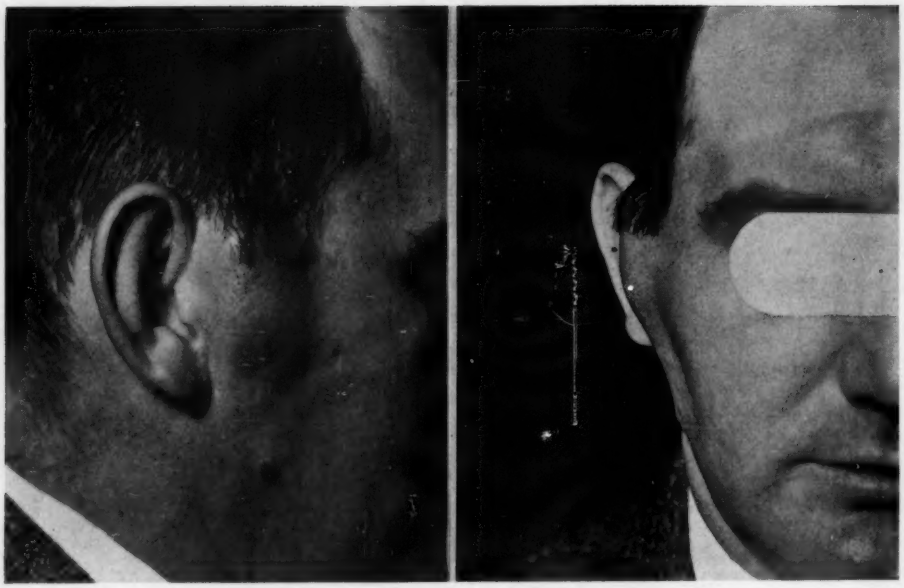

Fig. 1.—Photographs of E. W. before operation.

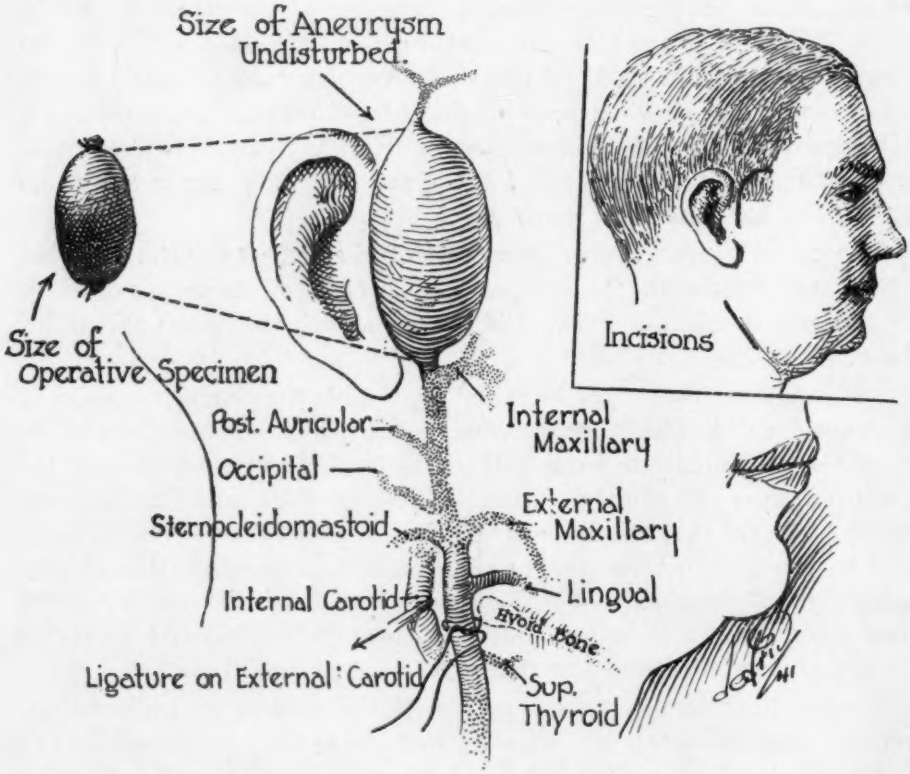

Fig. 2.—Schematic drawing showing in solid lines the vessels that were seen at operation.

doubtful. Circoid and arteriovenous aneurysms are quite different from the condition we are studying. At least some of the cases of post-traumatic aneurysm differed from pulsating hematomas only in duration. It is well known that syphilis causes aneurysms of only the great vessels; no case of temporal aneurysm has been considered of syphilitic origin. There have been other recent reports but we have been unable to find records of any cases of spontaneous true aneurysm of this artery other than the nine listed by Winslow and Edwards.

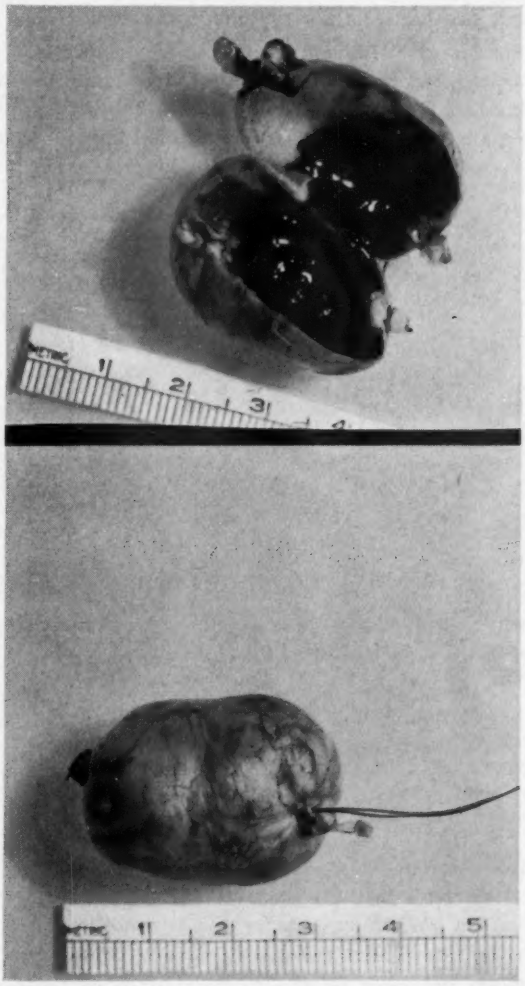

Fig. 3.—Photographs of the pathologic specimen whole (below) and bisected (above), and a centimeter rule.

CASE REPORT.—E. W., male, Caucasian, aged 34 years, was admitted to the hospital, May 6, 1939. About five years before, the patient had noticed a small swelling just in front of the right ear. The size increased with gradual acceleration; it was only about one-half its present size a year before. There was no pain and no symptom of any kind other than the presence of tumor. The size seemed to decrease somewhat with rest. There were no history of injury, no illnesses during the past ten years, no venereal infections. In 1929, he was in another

hospital for drainage of a small submental "abscess" and for circumcision. The only other known illness was scarlet fever at the age of 4 years.

Physical examination showed nothing remarkable except for the tumor which measured about 5.7 by 3.0 by 2.5 cm. (Fig. 1). There were no visible pulsations but upon palpation a definite expansile pulse was felt. It was not attached to the skin. The upper pole could be moved a little over the temporal fascia and the zygoma, but the lower pole seemed fixed. There was no audible bruit. Upon pressure, it would disappear; when released, it would expand again quickly (perhaps one to two seconds) with a soft palpable swish.

The blood pressure readings were 136/78 and 110/82. The laboratory studies, including complement fixation tests for syphilis, were negative.

Operation was performed with open cone ether anesthesia. Using the great horn of the hyoid bone as a guide, an oblique incision was made in one of the skin creases of the neck. Both the internal and external carotid arteries were exposed. After demonstrating that compression of the external carotid made the aneurysm softer and slower in refilling, it was ligated with black silk No. 8 (Fig. 2).

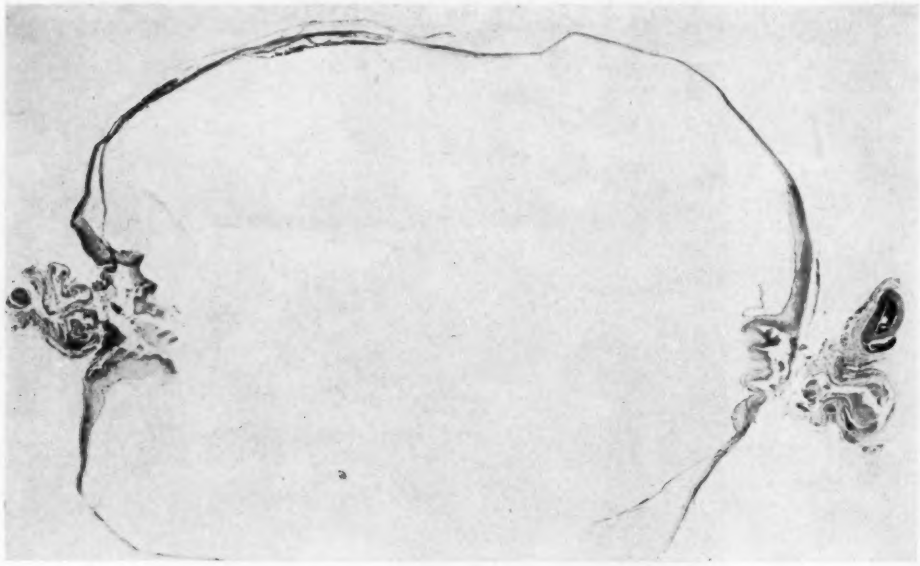

Fig. 4.—Photomicrograph of the wall of the aneurysm.

A second incision was curved over the superior and posterior surfaces of the aneurysm with its lower end just in front of the tragus. The aneurysm was situated superficial to the zygomatic process of the temporal bone, extending up over the temporal fascia, and down into the parotid gland. It was of the fusiform type, thin-walled throughout and very elastic. The artery above was clamped, ligated, and severed. Then, while deep pressure was applied with a finger behind the neck of the mandible in the region of the bifurcation of the external carotid artery, the aneurysm was easily isolated by sharp and blunt dissection. The only arterial communications were at the upper and lower poles; no auricular, transverse facial, or zygomatico-orbital branches were seen (Fig. 3). The artery at the lower pole of the aneurysm was also ligated with black silk No. 8.

The wound of the face was closed by stitching the subcutaneous layer with fine plain catgut and the skin with black silk. The wound in the neck was closed by sewing the platysma with chromic No. 00 and the skin with black silk.

The dressings were padded with cotton and a firm figure-of-eight bandage was applied about the head and neck.

The convalescence was uneventful. Four days after operation the larger skin stitches were removed and the patient was allowed to leave the hospital. There were no symptoms or signs of local circulatory deficiency nor was there any interference with nerve function.

The pathologic specimen measured 3.2 by 2.1 by 2.1 cm. (Fig. 3). It contained recent blood clot. Microscopic sections of the wall of the aneurysm showed uniformly thinned media (Fig. 4).

DISCUSSION

The patient presented himself for treatment only because of the enlarging tumor; there was no pain and no other symptom. Operative incisions were placed to give adequate exposure and at the same time leave no noticeable scars. It might seem that the neck operation with ligation of the external carotid was unnecessary. The rapid filling of the aneurysm after compression and the proximity of the facial nerve led us to take this precaution. Ligation distal to the origin of the lingual artery probably would have reduced the blood flow into the sac more effectively.

The extreme elasticity of the thin-walled aneurysm was a striking feature of the operative findings. The volume of the specimen as it was removed was apparently only about one-third the volume of aneurysm before interference (Fig. 2). The sac was immediately surrounded by loose connective tissue; its removal was easy.

SUMMARY

Aneurysm of the temporal artery is a rare condition which is usually post-traumatic. Our case of spontaneous true aneurysm is apparently the tenth case of its kind to be reported. Cure was easily and safely effected by excision after ligation of the external carotid artery.

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END-TO-END ILEOCOLOSTOMY: INDICATIONS FOR, AND EVALUATION OF, IN RESECTION OF RIGHT PORTION OF COLON IN ONE STAGE FOR MALIGNANT LESIONS

CHARLES W. MAYO,* M.D., AND CARL P. SCHLICKE,† M.D.
ROCHESTER, MINN.

IT IS generally agreed that the procedure of choice in dealing with operable malignant lesions of the right portion of the colon is radical removal of that portion of bowel which lies between the terminal portion of the ileum and the middle of the transverse colon, together with removal of the associated gland-bearing tissues. However, agreement as to the best means of accomplishing this end safely and expeditiously and of restoring continuity of the bowel is not general. It is our belief, as it is the belief of many other surgeons, that it is futile to attempt to standardize resection of the right portion of the colon and the procedure to be carried out must be adapted to the patient. We consider as unsound all dogmatic statements made in regard to the questions of whether operation should be carried out in one, two, or more stages, the type of anastomosis that should be established, and the type of suture that should be employed. Advocates of various methods are in the habit of ascribing such success as they have achieved to some particular measure which they have devised or employed. Actually, success in management of these cases depends on a multitude of factors, including selection of patients and preoperative and postoperative care. Surgeons are ill advised who feel that one particular step or method is all important or indispensable.

It is our purpose to review briefly the background of the problem and to describe a method of operation which we have found satisfactory in certain cases.

BACKGROUND

Early resection of the colon was less radical than that customarily employed today and consisted of resection of the tumor-bearing region and immediate performance of end-to-end anastomosis. In 1879, Baum carried out such a procedure for a lesion of the ascending colon in a case in which ileostomy had been performed for obstruction eight weeks previously. The patient died nine days after resection was performed. Later in the same year, Kraussold removed the ileocecal coil from a patient for carcinoma and performed anastomosis between the terminal portion of the

*Division of Surgery, Mayo Clinic.
†Fellow in Surgery, Mayo Foundation.
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ileum and the ascending colon. Similar operations were attempted by Billroth in 1881, and von Bergmann in 1882, but it remained for Maydl, in 1883, to perform the first successful resection of the cecum. In his case, resection was preceded by ileostomy, which, six months later, was converted into an ileocolonic stoma. The patient died in the course of a year from recurrence. The next year Billroth reported a successful case in which primary end-to-end anastomosis had been performed; in 1885, similar reports were published by Hofmokl and by von Bergmann. Barton, in 1888, was the first to report successful resection in this country, but he was never able to rid his patient of the artificial anus which he had established.

As more of these operations were performed, it soon became apparent that they left much to be desired. This was true of operations on all portions of the colon. In 1889, Franks collected fifty-two cases of "colectomy" from the literature and found that the mortality rate was 40.8 per cent. His studies led him to conclude that, because of the poor survival rate, the operation was a failure as a curative agent for malignant disease but that it should be performed whenever possible because of the symptomatic relief it afforded. As he found no difference between the mortality rate following immediate suture and that following establishment of an artificial anus, he advocated closure in order to eliminate a second operation.

Recognition of these poor results led to an active search for better methods of handling the problem. The chief hazards were peritonitis and shock. Some of the early operations took four or five hours to perform and required innumerable sutures, which defeated the purpose that they were intended to serve. Contamination might occur at the time of operation as a result of accident or careless technique, or, later, because of a faulty suture line. Efforts toward improvement by a quick, safe method lay in several directions. The first was to keep all manipulations of the bowel outside the peritoneal cavity. This was the principle of exteriorization, employed of necessity by Maydl, Schull, and von Volkmann, of design by Bloch, Paul, and von Hochenegg and publicized by Mikulicz. It found its widest application in operation for lesions situated in the sigmoid, but it recently has been warmly advocated by Lahey and his associates in operation for lesions in the right half of the colon as well. The relative speed and simplicity of this type of operation also aided in reducing the occurrence of shock. However, those who found the idea of an artificial anus repellent strove to find a method which would combine the safety and speed of exteriorization with the obvious advantages of primary anastomosis. The old method of suture was felt to be too time-consuming and uncertain. Countless tricks and gadgets were tried to facilitate anastomosis. Among these were McGraw's elastic ligature, Murphy's button, Madelung's cartilage plates, Seim's bone plates, Ullman's carrot bobbin, Pilcher's potato bobbin, Starr's rubber

tube, invagination rings and so forth. The extent to which these devices aided in making anastomosis safer is attested by such studies as that of Magill, who, in 1894, made the first thorough review of the literature on resection of the ileocecal coil. He found that the mortality rate was lowest in the hands of surgeons who used these devices and that the mortality rate and incidence of fecal fistula were highest in cases in which suture anastomosis was employed. Littlewood found that anastomosis could be performed in ten to fifteen minutes, in contrast to the lengthy earlier operations.

As these devices simplified anastomosis and, by their function, minimized late leakage, attempts were made to reduce the last major hazard, namely, contamination of the peritoneal cavity with contents of the bowel at the time of operation. This was the search for a completely aseptic anastomosis. Initiated by the experiments of Halsted, in 1887, the crusade was carried on with the suture overclamp method of O'Hara, the Parker Kerr basting stitch, and the countless modifications of aseptic clamps which Rankin and others[29] have devised.

The final road along which safety in operations on the right half of the colon was sought was the operation in multiple stages. Following the first successful exclusion by Trendelenburg in 1885, this operation was employed at first only as a palliative measure to circumvent obstruction. Later it was performed as a preliminary step to subsequent resection. By this method the unpleasant features of an artificial anus were avoided, and, by establishing anastomosis at one operation, resection subsequently became less hazardous.

As more patients began to survive the operation and to die from recurrence, the cause for the failure of resection to effect a cure was sought. In the early operations, only the growth and the immediately adjoining portions of bowel were removed. By taking out more bowel and exercising care to remove adjacent lymph nodes, it was found that the survival rate could be increased. The present pattern for resection was established by Friedrich, in 1904. He advocated removal of several inches of the terminal portion of the ileum, the cecum, appendix, the ascending colon, hepatic flexure, and the first third of the transverse colon, along with the regional lymph nodes. Friedrich performed this operation in one stage, uniting the terminal portion of the ileum to the transverse colon by a side-to-side isoperistaltic anastomosis. The rationale of this type of procedure was summarized by Cheever, in 1931. He pointed out that removal of a smaller portion of the colon did not give a wide enough margin of safety, that the proximal portion of colon, being incompletely covered by peritoneum, was less amenable to anastomosis, that the rich blood supply of the ileum minimized the liability to necrosis at the suture line, and that the operation was relatively easy. The importance of radical removal of the ileocolic lymph vessels and nodes en masse with the growth was emphasized by Dobson and Jamieson, who made a pains-

taking study of the lymph vessels and nodes in this region. They advocated removal of all glands receiving direct vessels up to the gland by the duodenum at the origin of the ileocolic artery, which they felt was the highest "primary" gland.

VARIOUS PROCEDURES

Although the actual resection of the colon now has become well standardized, the remainder of the operation has not, since it may be performed in one, two, or more stages and by various types of technique. A brief review of these methods with some of their advantages and disadvantages may be worth while.

Operation in Multiple Stages.—Operation in multiple stages, including exteriorization of the segment of bowel which contains the growth, removal of this segment, application of clamps to the spur, and closure of the residual stoma, has been practiced most widely at the Lahey Clinic. Carter, Slattery, and Hahn, Patterson and Webb, and others have written of its virtues. It was stated that it afforded the least danger of peritonitis and the greatest safety to the patient, since there is no fear of leakage or contamination. According to Lahey, the large bowel, because of its sacculated walls, scanty blood supply, virulent bacteria, bands and appendages, is unfavorable for suture. Exteriorization probably is the simplest method of handling the problem, but the results have not been too successful in all hands. The excoriating ileal discharges, the degree of infection of the wound, the incidence of postoperative hernia, the long morbidity, and the necessity for many operations have led many to condemn it. Rankin[28] stated that the Mikulicz procedure is followed by recurrence in the abdominal wall in 12 per cent of cases. The limitations of the method were described by Sistrunk, who pointed out that it was applicable only to mobile or easily mobilized parts associated with a resectable mesentery, and that it was not suitable for large or adherent growths with infection or those associated with obstruction. Similarly, it was technically unsatisfactory in cases in which the patients were obese or in which a short mesentery was present. When used in such cases, carcinoma or infection was likely to invade either the wound or the peritoneal cavity.

Operation in Two Stages.—Wakeley and Rutherford stated that lateral ileocolostomy followed by resection ten to fourteen days later is the correct procedure for growths situated in the right portion of the colon. Many surgeons agree. Pemberton and Whittaker felt that such a course lowered the mortality rate and increased the operability. Infection about the growth subsides and obstruction is relieved after diversion of the fecal current. There is less reaction after resection as this is carried out in a separate compartment, formed by the adhesions of the first operation. Dixon and Priestley stated that the severity and shock of the operation are reduced by the two-stage procedure and that the second operation

is safer because of autovaccination which takes place during the first procedure. They pointed out that if death occurs after resection in one stage, it is questioned, in retrospect, whether a procedure of less magnitude could have been adopted. Although this is true, questions also arise when death occurs after operation in two stages. Ransom, in reviewing the material at the University of Michigan, concluded that operation in two stages was the safest procedure, since the amount of manipulation carried out at one time was less. He found that the time involved actually was not any longer because these patients had a smoother convalescence, and, since malignant tumors of the colon were slow growing, there was no added hazard because the tumor was left in the body longer. Allen reached a similar conclusion on reviewing the material at Harvard University. Rankin[28] felt that in any event it was the best procedure for surgeons who did not have special training in this field. On the other hand, Lovelace and one of us (C. W. M.),[21] in a review of 885 cases encountered at the Mayo Clinic, in 67 per cent of which resection was carried out, found that the mortality rate was 6.7 per cent higher and the hospital stay twenty-four days longer following operation in two stages than in cases in which operation was carried out in one stage. The low mortality rate reported by the numerous advocates of operation in two stages may be owing to their failure to include deaths which occurred after the first stage of the operation. Furthermore, the short interval between stages advised by numerous writers is seldom feasible in actual practice.

Operation in One Stage.—Operation in one stage is the operation of pioneers in this field. Condemned for many years because of its dangers, the trend now is back toward it, as Rankin[28] pointed out, because of the better preparation and selection of cases and the increasing experience of surgeons. Moynihan, Wilkie, and Lockhart-Mummery in Great Britain, and Harvey, Andrews, Cheever, and MacFee in this country, have advocated its use widely. Rankin[28] stated early that it was applicable in about one-half of the cases without increased risk. Stone and McLanahan, who formerly advocated operation in more than one stage, now favor operation in one stage.

The advantages of operation in one stage are many. The patient is subjected to only one operation and one anesthesia, with their attendant risks. Stay in the hospital is shorter and the time that the tumor remains in the body is reduced. This, according to Lovelace and one of us (C. W. M.), is reflected in an increase of 2.5 per cent in the five-year survival rate. Resection is technically easier since the surgeon is unhampered by the adhesions of a previous operation. Since resection has to be performed, it might as well be at the first operation, as restoration of continuity of the intestinal tract constitutes only a minor part of the operation. Although most of its advocates urge its use for patients in good condition, there are those who would use it only as a palliative

measure in cases in which the patient is debilitated and bleeding and who probably could not stand more than one operation. Rankin,[28] Jones,[14] Wangensteen, Campbell, MacFee, and Stone and McLanahan have advocated anastomosis by the so-called aseptic technique. Bell and Henley and many other surgeons now perform open anastomosis, occasionally employing a basting stitch.

Continuity of the bowel may be restored by end-to-end, end-to-side, or side-to-side anastomosis. Each method has its advocates; Allen stated that this consideration is of no importance. End-to-end anastomosis is technically the simplest to perform; there is only one suture line and no blind ends are left. It has been stated that leakage is likely to occur at the mesenteric juncture because the space where the mesentery splits is devoid of peritoneum, but, according to Rankin and co-workers,[29] faulty cutting or clamping, without adequate regard of blood supply, more often is the real cause of leakage.

It has been stated that side-to-side anastomosis forms the strongest anastomosis and that vascularity is assured by supplement from the ileum. On the other hand, the blind ends, especially if left too long, may form reservoirs for the accumulation of waste. Whether the abolition of peristalsis produced by cutting the circular muscle fibers is of practical importance is doubtful.

The end-to-side anastomosis is said to simulate most nearly the normal ileocolic relationship. In operations carried out in more than one stage, it affords better bipassing of the fecal current but may prove dangerous if obstruction develops.

Each of these methods has its proper place. It is when one method only is employed, to the exclusion of others, that an injustice is done to the patient.

In the presence of acute perforation or in certain cases in which a lengthy operation would tax unduly the strength of a seriously ill patient, exteriorization and the operation performed in multiple stages can be used to great advantage. In cases of localized perforation and high grades of infection, preliminary short circuiting greatly facilitates and adds to the safety of subsequent resection. When obstruction exists, preliminary decompression is the primary consideration. If this cannot be achieved by medical means and if dilatation is not great, the bowel should be decompressed by a short circuiting operation. If distention is great, ileostomy or cecostomy are the procedures of choice. Under no circumstances should resection in one stage be carried out under such conditions, and, in the presence of a dilated, edematous bowel, undue manipulation and attempts at anastomosis are unwarranted. However, in the case of a patient who is well prepared preoperatively, who seems to be standing the procedure well, and whose growth is found to lend itself readily to resection, we feel that resection and anastomosis in one stage is the ideal course to follow. As to the means by which anastomosis

should be carried out, the findings of Lovelace and one of us (C. W. M.) are of interest. In a review of the cases in which resection in one stage was performed at the Mayo Clinic, it was found that the mortality was 23.4 per cent when end-to-side anastomosis was performed; 22.7 per cent when side-to-side anastomosis was performed, and 19.2 per cent when end-to-end anastomosis was carried out. It is this finding that prompted our interest in this technique and led to the present study.

It long has been felt that if operation in one stage is performed, a safety valve should be provided by performing enterostomy to insure against tension on the suture line caused by the collection of gas and waste. This has been an almost inviolable rule with Rankin and associates,[29] Jones,[15] and Judd. Stone and McLanahan found it seldom performed in their series of cases but felt that it should be performed more often. Cheever felt that it did no harm. Wilkie and Lockhart-Mummery felt that it might be better to perform an operation in two stages rather than perform enterostomy. Harvey condemned the procedure as a source of infection and fecal fistula from leakage around the tube; he felt that an inlying rectal tube came nearer to accomplishing the desired result. Ransom found a much higher mortality rate in both palliative and curative operations when enterostomy was performed. Lovelace and one of us (C. W. M.) reported a similar observation.

CASES IN WHICH END-TO-END ILEOCOLOSTOMY WAS PERFORMED AT THE MAYO CLINIC

The present study is based on a review of all cases encountered at the Mayo Clinic in which resection of the right portion of the colon with end-to-end anastomosis of the ileum and colon was carried out for malignant disease. Ninety-six such operations were performed by eight surgeons prior to Jan. 1, 1942. There were eighteen hospital deaths, a gross mortality rate of 18.8 per cent. The average stay in the hospital of patients surviving operation was 20.3 days. In forty-two cases, Witzel enterostomy was carried out as a "safety" measure. The mortality rate in this group was 28.6 per cent. The average stay in the hospital was 22.5 days. In the fifty-four cases in which enterostomy was not established, the mortality rate was 11.1 per cent and the average stay in the hospital was 18.9 days (17.7 days if one patient who stayed in the hospital seventy-seven days is excluded).

This operation was used most frequently at the clinic in the decade of 1917 to 1927. However, as the surgeons became wrongly but increasingly aware of the need for enterostomy, the mortality rate increased until the operation finally was discarded; only two such operations were performed in the next ten years. However, as a result of the review by Lovelace and one of us (C. W. M.), it again has come into frequent use, but without supplementary enterostomy. At the time of this writing, this operation

has been carried out in twenty-seven cases on the service of one of us (C. W. M.) with only one death, that of a man 82 years of age.

Technique of Operation.—The anesthesia is adapted to the patient; in most cases spinal anesthesia, supplemented by pentothal sodium, is found satisfactory. The abdomen is opened by a right rectus incision, the muscle being retracted mesially within its sheath. The liver is palpated carefully for evidence of metastasis. Metastasis is found in about 10 per cent of cases of carcinoma of the right portion of the colon in which exploration is performed. The entire colon then is examined in order to determine whether other tumors are present. They may be expected in about 6 per cent of the cases. The lesion then is examined carefully and its size, situation, and mobility are determined. Regional lymph nodes should be palpated, although the decision as to their involvement rests with the pathologist. Resection then should be planned so that in its execution there will be no difficulty in effecting adequate removal and subsequent anastomosis.

The cecum is elevated and retracted mesially, and mobilization of the right portion of the colon is effected by incision of the lateral peritoneal reflection. By blunt dissection the colon and its mesentery are mobilized almost to the midline, care being exercised to avoid injury to the retroperitoneal portion of the duodenum and the right ureter. A wide segment of mesentery is resected to remove the lymph vessels and nodes draining this region. The mobilized segment of bowel is placed outside the peritoneal cavity and is walled off with moist sponges. The ileum and transverse colon are cut across; usually about 6 inches (15 cm.) of ileum and about a third of the transverse colon are removed. For lesions of the hepatic flexure, more of the transverse colon is removed. The segments to be used for anastomosis are grasped with rubber-shod clamps and division is effected with the cold knife. The use of crushing clamps or cautery on segments to be used for anastomosis seems inadvisable as anastomosis is more likely to succeed in healthy normal tissue than when crushed tissue with thrombosed blood vessels is used. As emphasized by Lockhart-Mummery, both the large and small bowel should be divided obliquely. The small bowel is divided obliquely in order to compensate for the disparity in size which exists between it and the large bowel; the large bowel is divided this way in order to insure an adequate blood supply to its entire circumference. If the opening in the ileum requires further enlargement, this can be achieved by a longitudinal cut along the antimesenteric border, the edges being rounded off. The mucosa is swabbed with tincture of merthiolate.

The rubber-shod clamps are approximated, the wound is walled off carefully with moist sponges, and the posterior row of sutures is inserted in the form of a continuous silk stitch. The posterior suture of catgut in the mucosa then is inserted, the corner is rounded carefully, and the anterior borders are approximated with an inverting stitch of the base-

ball variety. The rubber-shod clamps are removed and the outer row of silk sutures are inserted. Nearby epiploic tags are drawn over the anastomosis for added security. The cut edges of the mesentery are approximated, care being taken not to jeopardize the blood supply at the line of the anastomosis. The raw surface of the interior portion of the abdominal wall is then covered with peritoneum as well as possible. Raw surfaces and traps should be eliminated. In ideal cases drainage is unnecessary. In the usual case, one or two soft rubber drains are inserted through a stab wound in the right flank into the retroperitoneal space. Occasionally a strand of silk is left attached at the site of anastomosis and is brought out through the abdominal incision to serve as a guide for drainage. Tincture of merthiolate is used liberally, and, recently, it has been our practice to insert 75 gr. (5 Gm.) of sulfanilamide powder into the peritoneal cavity before closure. Before the patient is taken from the operating room, the anal sphincter is temporarily paralyzed by thorough dilatation. This procedure has been found to be as effective as an inlying rectal tube in preventing retention of gas and feces by the sphincter.

The following variations were noted. Anastomosis by the aseptic method was performed in three of the ninety-six cases. Many of the aseptic methods are complex and time consuming. The designation "aseptic" may lull the surgeon into a false sense of security and cause him to forget more important fundamentals. Even after aseptic anastomosis, bacteria usually can be cultured from the line of suture. Crushing and burning tissue does not enhance its value for anastomosis. The sutures are carefully placed, including, as Halsted demonstrated, the submucosa in each stitch and avoiding large numbers of sutures. As Wilkie pointed out, numerous sutures kill tissue and furnish a culture medium for anaerobes. Avoidance of tension, judicious reinforcement, and, especially, attention to blood supply accomplish more than employment of a multitude of gadgets. Late leaks, rather than contamination at the time of operation, account for most deaths. In one of the early cases, anastomosis was carried out over a rubber tube.

Perforating growths often require more extensive resection. Part of the abdominal wall had to be removed in three cases and the parietal peritoneum in a large number. Several feet of adherent ileum were removed in three cases and a loop of sigmoid was removed in another. In two cases resection of outer coats of the duodenum and portions of the pancreas was performed. Additional procedures, such as herniorrhaphy, myomectomy, and insertion of a tube for radium were carried out in one case each. In seventy-six cases, however, the operation was carried out largely as described, and it was only in the early cases that the most complicated situations were treated in one stage.

As pointed out previously, enterostomy was carried out almost routinely in many of the early cases. We feel, however, that enterostomy

not only is unnecessary but actually is hazardous and adds greatly to the risk of operation. If the surgeon does not like the appearance of the bowel or does not trust the anastomosis, he should perform the operation in multiple stages and not feel that everything is set aright by placing a tube in the ileum.

When we discovered the striking differences in mortality rates which existed in the cases in which enterostomy had been performed and those in which it had not, we thought perhaps this might be due to the fact that enterostomy had been performed on the patients who were sicker, who had obstruction, or who had undergone extensive operations. A review of the cases disclosed that this was not true, that the two groups were comparable in every way, and that the only factor which should be held accountable for the increase of 17.5 per cent in the mortality rate was the enterostomy. As a substitute for enterostomy, it is advisable to dilate the anus thoroughly immediately after operation in order to paralyze temporarily the external sphincter.

Selection of Cases and Findings at Operation.—In the early days of the operation there seems to have been little selection of cases. The operation to be performed depended largely on the whims or inclination of the surgeon; whether he added enterostomy was largely a matter of personal conviction, some surgeons performing it routinely and others occasionally.

The patients in this series of cases were between 15 and 81 years of age; the average age was 53.9 years. Sixty-seven of the patients were men and twenty-nine, women. At the time of operation, fifty-eight patients were thought to be in good general condition, fourteen in fair condition, and twenty-four in poor condition. Complicating conditions, such as goiter, old tuberculosis, cardiac disease, or arteriosclerosis, were present in fifty-one cases. Two patients had amebic dysentery and eleven had undergone abdominal operations within six months previous to operation. A toxic goiter was removed from one patient a week before operation on the colon was performed. Obesity was marked in several cases; nearly all patients had anemia of some degree and a third had severe anemia. Half of those who had severe anemia required transfusion before operation. Many patients had lost weight, a fourth of them having lost more than twenty-five pounds (11.3 kg.). Slight evidence of obstruction was noted in four cases and eight patients gave a history of recurrent obstruction.

The tumor was a carcinoma in ninety-three cases and a sarcoma in three. The lesion was situated in the cecum in fifty-nine cases, in the ascending colon in twenty-eight, and in the hepatic flexure in nine. In 51 per cent of cases there was neoplastic extension through the wall of the bowel which had involved the serosa, abdominal wall, or adjacent bowel. Inflammatory fixation had occurred in sixteen more cases, so that in only thirty-one cases was the growth freely movable and of type A, according

to Dukes' classification. Regional nodes were involved by metastatic implants in 52 per cent of the cases. There was questionable involvement of the liver in three cases and definite involvement in one. In eighty-nine cases operation was performed with the hope of cure; in seven cases operation was palliative because of involvement of lymph nodes, local peritoneal extension which could not be removed, or metastatic deposits in the liver. Adenomatous polyps were noted in three cases, in one of which malignant degeneration had occurred. Metastatic nodules were found in the mucosa of the ileum, cecum, and ascending colon in one case. At the time of operation the small intestine was dilated in eight cases and the large intestine in one.

In general, care in the selection of cases has increased. Patients should be in fairly good general condition and should not have objective evidence of obstruction or of marked inflammatory reaction about the growth if operation is to be performed in one stage.

Preoperative and Postoperative Care.—In the early cases, the patients were admitted to the hospital, given an enema, and, occasionally, a dose of castor oil and then submitted to operation. Now great care is taken to cleanse the bowel and to improve the general condition of the patient. When resection in one stage is anticipated, vaccine is given intraperitoneally. After operation each patient is placed in an oxygen tent and given 500 c.c. of citrated blood. Fluids are administered parenterally, the oral route being prohibited until the patient begins to pass gas by rectum. Frequent insertion of glycerin suppositories and tubes into the rectum facilitates the passage of gas.

Complications.—Infection of wounds was the most common complication among the patients who survived operation; it occurred in twenty-eight cases. Infection of wounds has been less frequent since the use of sulfanilamide. This and other complications were common among patients who underwent enterostomy. Fecal fistula developed in only two cases. All fistulas caused by enterostomy tubes closed spontaneously. Pulmonary complications were infrequent among patients who survived operation; atelectasis and pneumonia occurred in one case each, and pulmonary infarction in two cases. Ileus occurred in three cases, in one of which it was necessary to perform ileostomy. Cystitis was noted in seven cases. Low grade inflammatory processes about the site of an anastomosis, which gradually disappeared, occurred in three cases. Parotitis developed in three cases and submaxillary mumps in one.

Cause of Death.—General peritonitis was the most common cause of death in the series. It accounted for fifteen of the eighteen fatalities. In two of these cases, pneumonia also was present and in one, pulmonary embolism occurred. In eleven of these fifteen cases, ileostomy had been performed. Local peritonitis was the cause of death in two cases; it was associated with ileus in one case and with acute endocarditis and pul-

monary infarction in the other. In one of these two cases, enterostomy had been performed. One man, 82 years of age, died of bronchopneumonia.

SUMMARY AND CONCLUSIONS

There are many methods for dealing with carcinoma of the right portion of the colon. We have reviewed a number of these methods, together with their background and development. Resection with end-to-end ileocolostomy in one stage is a method which has been found satisfactory in certain cases. This operation has been performed at the Mayo Clinic ninety-six times, with eighteen deaths. In forty-two cases complementary enterostomy was performed; the mortality rate in this group was 28.6 per cent. In the fifty-four cases in which enterostomy was not performed the mortality rate was 11.1 per cent. We now regard enterostomy not only as unnecessary but also as an added hazard in conjunction with resection and anastomosis in one stage. If the surgeon has any misgivings, operation in two stages is preferable to the performance of enterostomy.

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DOUBLE LOOP RECTAL RESECTOR AND BIOPSY FORCEPS

ROBERT TURELL, M.D., NEW YORK, N. Y.

THE instrument illustrated in Fig. 1 is designed for the endoscopic electric resection of rectal papilliferous new growths as well as for the removal of specimens for histologic studies. This instrument is especially useful for the extirpation of large, broad, sessile adenomas when the looping of the pedicle with the ordinary single wire loop snare is either technically impossible or unsafe.

The instrument consists of a pair of removable tungsten wire loops mounted at the distal end of an insulated shaft and actuated by forceps handles. The proximal loop transmits the cutting current and meshes into the stationary, inactive distal loop which is slightly larger. The proximal loop travels a maximum longitudinal distance of 2 cm. parallel to the shaft of the instrument.

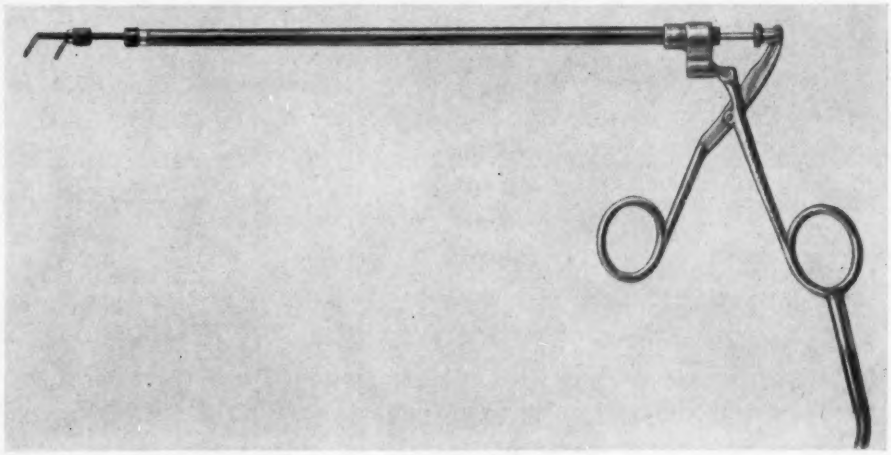

Fig. 1.—Lateral view of instrument.

The shaft with the loops has a rotating mechanism near the handle which permits rotation of 360 degrees, akin to that I have already described.[1] Thus, by rotating the shaft of the instrument, the loops can be made to face a suspected lesion located anywhere on the circumference of the terminal towel.

Since the loops are constructed of wire, they offer no appreciable obstruction to vision and thus the lesion remains in full view during

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resection. The light construction of the loops is made possible by the apparent absence of resistance of the tissues to the cutting current.

To remove a tumor, the open loops are placed upon the neoplasm; the desired cutting current is applied and the loops are closed as illustrated in Fig. 2. These maneuvers are repeated until all the intraluminal

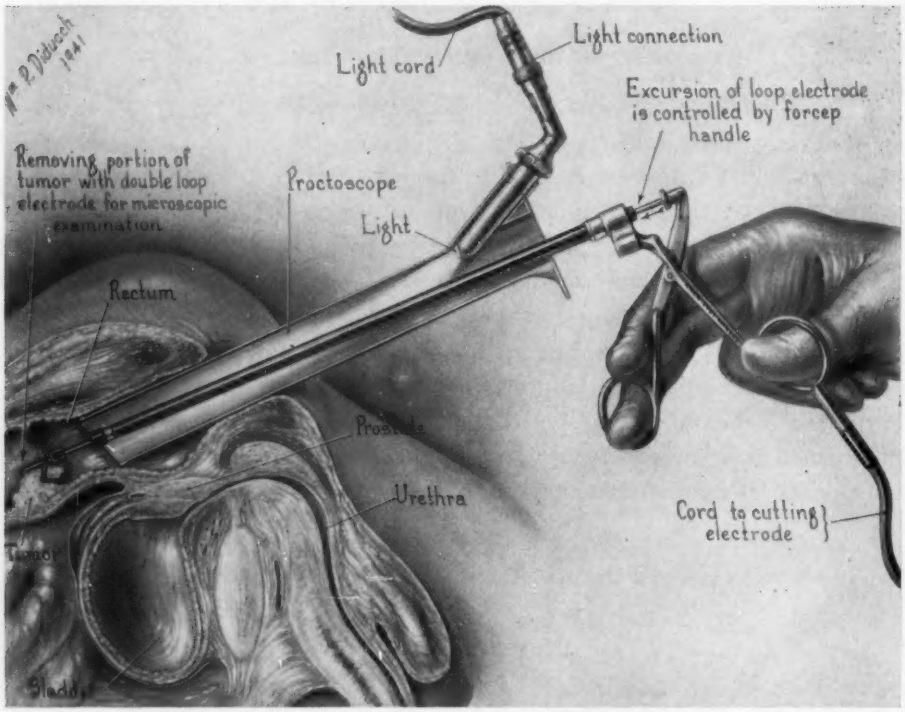

Fig. 2.—Sagittal section showing removal of portion of tumor; note the travel of the proximal active electrode.

projections of the neoplasm are resected; the base of the tumor may be coagulated at the conclusion of the resection or at a later date. Bleeding is usually prevented by the hemostatic effect of the cutting current or it may be easily controlled by coagulation (with the same instrument) merely by substituting the coagulating for the cutting current.

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METHOD OF CLOSING THE PYLORO-ANTRAL POUCH IN THE ANTRAL EXCLUSION OPERATION*

OWEN H. WANGENSTEEN, M.D., MINNEAPOLIS, MINN.
(From the Department of Surgery, University of Minnesota Medical School)

FINSTERER, described antral exclusion as an alternative method of dealing with the difficult, indurated ulcer during the course of gastric resection for duodenal ulcer. In the same paper, Finsterer stated that the mucosa from the residual antral fragment might be removed at the same time. As recently as 1934, however, Finsterer insisted that it did not make any appreciable difference in the end result, whether the antral mucosa was removed or allowed to remain. At that time, he stressed extending the resection proximally, removing usually two-thirds of the stomach; also, he believed it important to attempt to obviate retrograde filling of the afferent jejunal loop of the gastrojejunal stoma. In 1934, Finsterer admitted an incidence of gastrojejunal ulcer in 6.4 per cent of the patients upon whom he had performed the antral exclusion operation. In the meantime (1940), apparently, Finsterer has adhered more consistently to the more extensive gastric resection and has become alert to the great importance of excising the mucosa from the residual antral pouch, even though he allows the pyloric sphincter to remain. With this practice, Finsterer has not observed the occurrence of gastrojejunal ulcer following the antral exclusion operation.

In 1926, the Dutch surgeon, Wilmanns, pointed out the importance of excision of the antral mucosa for the success of the antral exclusion operation for duodenal ulcer. Wilmanns stated that he had performed antral exclusion with simultaneous removal of the antral mucosa in difficult duodenal ulcers since 1923. He divided the antrum 2 cm. proximal to the pylorus and dissected out the antral cylinder of mucosa and closed the resulting seromuscular pouch. In 1931, Drüner, in a very brief paper, composed of two short paragraphs, mentions that he had performed such an operation, not unlike that described previously by Wilmanns. Independently, Bancroft (1932), in this country, described excision of the antral mucosa as a variant of the Devine exclusion operation for duodenal ulcer. In the preceding three and a half years, Bancroft had done fourteen such operations, all the patients making a satisfactory operative recovery. Bancroft states that he was led

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to perform excision of the antral mucosa as an adjunct to the Devine exclusion operation on the suggestion of Dr. L. G. Cole, who believed that removal of the antral mucosa would improve the results of the Devine operation. Bancroft's illustrations suggest that he removed the mucosa from about the distal one-third of the stomach, certainly from the entire antrum. He did not then recommend simultaneous resection of the corporic and fundic zones (actively secreting) of the gastric mucosa, as had Finsterer (1918) and Wilmanns (1926) previously.

In the intervening years, antral exclusion with excision of the antral mucosa, as an item in the operation of extensive gastric resection for duodenal ulcer, has gained in popularity among gastric surgeons. Edkins (1904) had pointed out, many years before that, the antral mucosa, although it did not itself secrete hydrochloric acid, augmented the secretion of hydrochloric acid from the corporic and fundic zones of the gastric mucosa. The operation of antral exclusion with excision of the antral mucosa, therefore, has a sound physiologic basis. The Edkins' hypothesis of hormonal control of the gastric phase of gastric secretion is probably correct only in part, for as has been pointed out previously,[13, 18, 19] the small gastric resection with complete removal of the antrum will fail to protect a patient from recurrent ulcer unless an accompanying extensive resection of the corporic and fundic portions of the stomach is done simultaneously.

In Germany, Bürkle-de la Camp (1933) and Plenk (1936) expressed enthusiasm over the antral exclusion operation and depicted technical features of the operation. Zukschwerdt and Horstmann (1936) named a number of German surgeons who had displayed an interest in the procedure.

The experience of Ogilvie (1938) with the antral exclusion operation has served to focus important notice on excision of the antral mucosa for the success of gastric resection for duodenal ulcer. It is now a matter of common experience among surgeons that leaving a small fragment of antral gastric mucous membrane may prejudice the result, even though extensive simultaneous excision of the corporic and fundic (actively secreting) mucosa is made. Two such patients have been observed in this clinic.[19]

Allen (1942) and Allen and Welch (1942) endorse the operation of antral exclusion with excision of the antral mucosa for difficult duodenal ulcers, when accompanied by simultaneous extensive gastric resection. They report thirteen instances in which the operation was done, with one death. They point out that, whereas the end results of this operative procedure parallel closely the splendid achievement of the more extensive operation in which pyloric sphincter and antrum are removed completely, the incidence of complications is greater and the postoperative convalescence may be considerably longer in the antral exclusion group. This experience parallels that of Finsterer (1940),

who admits a higher incidence of postoperative complications with the exclusion operation. Finsterer admits, too, that he finds it necessary to employ drainage quite frequently.

THE EXPERIENCE OF THIS CLINIC WITH THE ANTRAL EXCLUSION OPERATION

Somewhat more than four years ago, a plan was set up in this clinic to test the capacity of a number of operations for ulcer to reduce gastric acidity. As others (Ogilvie, 1938, and Allen and Welch, 1942), we learned, too,[19] to our sorrow, that antral exclusion without exenteration of the antral mucosa, even though accompanied by extensive gastric resection, was a poor operation for ulcer, in that it failed to protect the patient against gastrojejunal ulcer. When, however, excision of the antral mucosa was added (described as the 4a operation in this clinic, see Fig. 1), this procedure appeared to be equally as effective as the Group 3 operation (extensive gastric resection with excision of pylorus and antrum) in depressing effectively the secretion of hydrochloric

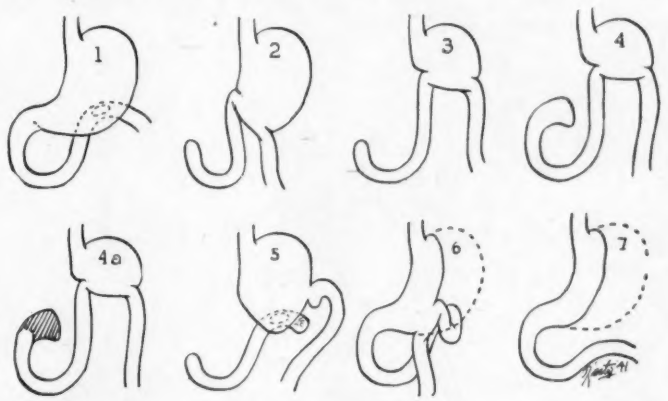

Fig. 1.—Types of operation subjected to scrutiny in this clinic. Fairly consistent achlorhydria attends only operations 3, and 4a. (Arch. Surg. 44: 48, 1942.)

acid and in ridding the patient of the ulcer diathesis. As a matter of fact, not a single stomal ulcer has attended either the Group 3 or 4a operation in this clinic. However, we experienced the same difficulties with the technical features of the 4a operation (antral exclusion and excision of antral mucosa) that Allen (1942) and Allen and Welch (1942) described. The first operation of this type was performed in this clinic in January, 1941. By August, 1941, thirteen such operations had been performed. Of this number, two developed a subphrenic abscess, necessitating surgical drainage (C. K., University Hospital No. 705300 and G. B., University Hospital No. 706376). In the instance of the latter patient, a drain had been placed beside the antral inversion. In both patients, the abscess formed beneath the left diaphragm, an occurrence emphasized previously by Carter. In two additional patients, the nature of the antral closure was such as to suggest the necessity for the employment of drainage. All the patients in the group recovered.

Inasmuch as our experience with duodenal closure in the Group 3 operation, whether done for gastric ulcer, cancer, or duodenal ulcer had been eminently satisfactory, it was obvious that the difficulty lay with the nature of the closure. In the first group, the closure was effected as shown in Fig. 2. Since then,[12] fifteen additional antral exclusions with simultaneous excision of the antral mucosa have been done as an incident in extensive gastric resection for indurated duodenal ulcer according to the plan shown in Fig. 3.

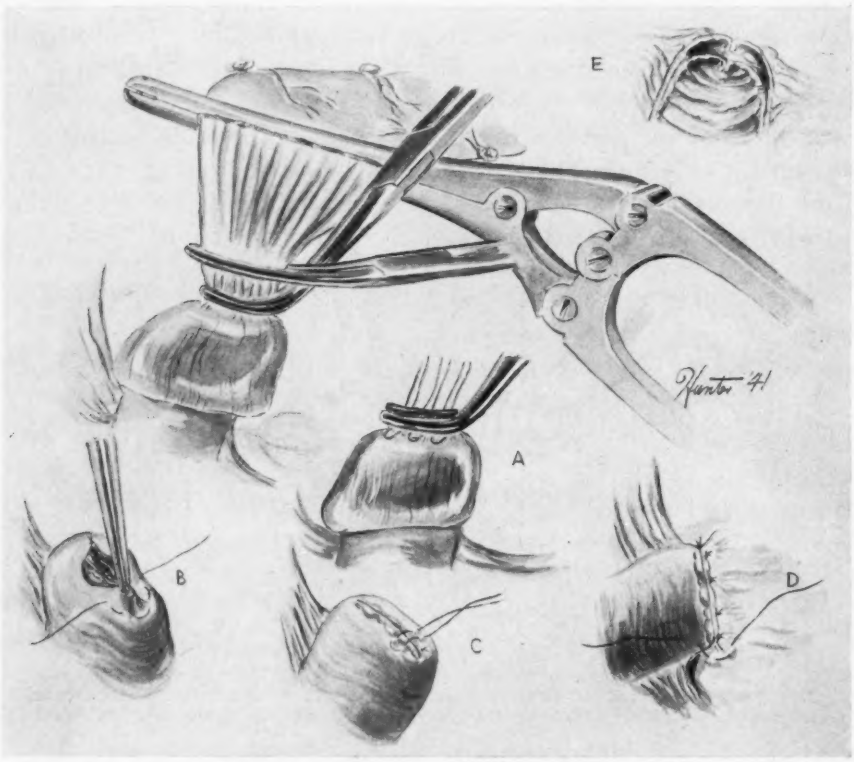

Fig. 2.—Technique of the antral exclusion operation as employed in the first series of cases; the procedure illustrated here probably conforms to standard surgical practice. The mucosa is clamped and divided at the pylorus. In *A* is illustrated the closure of the divided pyloric mucosa, which may be done with a running suture of catgut just as well. In *B*, *C*, and *D* are illustrated the technique of securing closure of the remaining seromuscular antral pouch by two inversion sutures; as a matter of fact, the matter is not as simple as illustrated here (see text), for the antral funnel narrows toward the pylorus. In *E* is shown another cause for failure of this type of operation, namely, persistence of a closed space. These two items, difficulty of inversion, and dead space make the usual method of closure of the pyloro-antral pouch unsatisfactory.

TECHNIQUE

The only essential difference in these two techniques of performing the antral exclusion operation relates to the manner of effecting closure of the resultant antral pocket denuded of antral mucosa. In both procedures, the mucosa at the pyloric valve was divided and closed with a running suture of catgut in an identical manner. In the earlier operations, closure of the residual antral pocket was accomplished by one or two inverting rows of interrupted silk sutures. Inasmuch, however,

as the remaining antral pouch narrows toward the pylorus like a funnel, it is obvious that satisfactory inversion of the peritoneal margins of the rim of the antral funnel may be very difficult and even impossible of nice and precise accomplishment without tension on the sutures. Another weakness of the inversion method of closure lies in the leaving of a dead space (Fig. 2*E*), an item to which Bancroft (1932) and Plenk (1936) had drawn attention; if this dead space is obliterated by sutures from within the pouch, the inversion, in turn, is made even more difficult. Finsterer (1940) employs two rows of inversion sutures to secure closure of the antral pouch after excision of the mucous membrane. Bancroft (1942) states that he has latterly employed triple inversion.

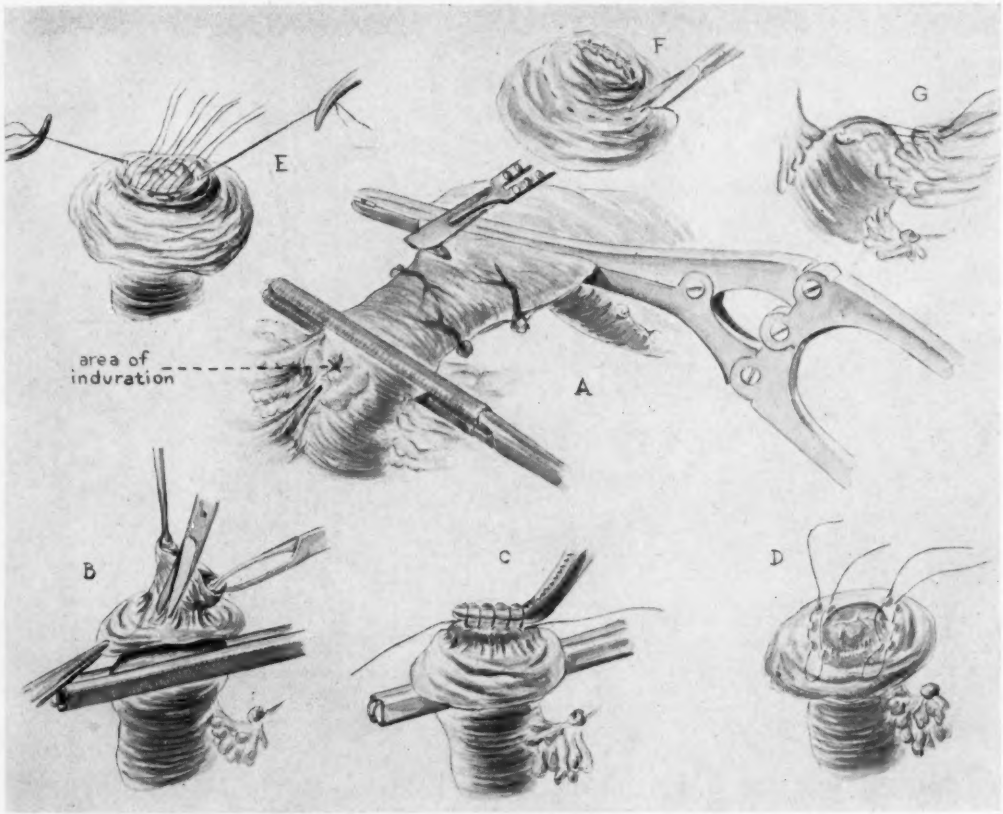

Fig. 3.—Technique of closure of the pyloro-antral pouch described herein and now in current use at the University Hospitals. *A*, Division of the antrum 4 to 5 cm. above the pylorus (usually slightly less than three fingerbreadths); a rubber-shod clamp just below the pylorus provides secure hemostasis during the dissection and the devascularization is carried up to the area of induration. *B*, Excision of the mucosa. *C*, Closure of the divided pyloric mucosa with running fine catgut. *D*, Approximation of the circular muscle by two 3—2 stitches (a Halsted mattress of fine silk with three bites coming and two returning); these stitches lend the effect of a half purse string. *F*, The circular muscle, to be approximated by Halsted mattress sutures of fine silk, is well shown here. F, The suture completed. Two rows of Halsted sutures may be placed; the dotted line indicates the site for excision of the superfluous seromuscular pouch. The rubber-shod clamp is removed at this part of the operation. *G*, The trimmed edges of the pouch have been approximated without inversion. (Interrupted Halsted mattress sutures of fine silk or a simple running stitch of catgut; finally, as shown here, the closure is capped with omentum or a margin of the right border of the transverse mesocolon.)

The difficulties related above suggested that the peritoneal inversion should be omitted altogether. During the past year (since August, 1941), the antral exclusion operation has been performed as shown in Fig. 3. The mainstay of this procedure, which, in our hands, has been uniformly successful, lies in a careful approximation of the submucous and circular muscle layers by a single row of interrupted sutures of fine silk, placed after the Halsted mattress pattern, immediately above the closure of the pyloric mucous membrane. In the lower portion of the antral pocket near the pylorus, the circular fibers of the muscle coat of the antrum stand out very prominently (Fig. 4), and appear, when

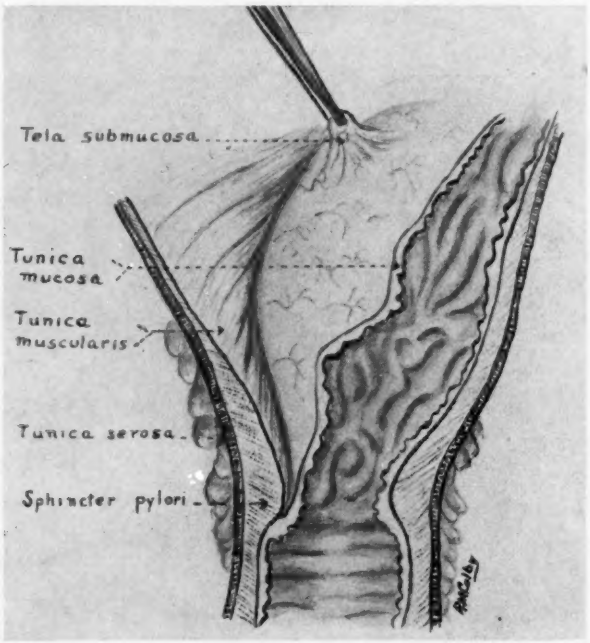

Fig. 4.—Drawing from a post-mortem specimen. A 10 per cent formalin solution was put into the stomach at autopsy, the duodenum and esophagus being ligated; after forty-eight hours of refrigeration this dissection was made. It is to be noted that the circular muscle is a well-developed muscle several centimeters proximal to the pyloric sphincter. This observation is well known to anatomists. It is approximation of these circular muscle fibers that is important in effecting an adequate and safe closure of the pyloro-antral pouch. Microscopic studies of the antral mucosa removed at operation indicate that the submucosa is removed with the mucosa.

viewed from the inside of the residual antral pouch, not unlike a sphincter muscle which, in fact, this circular muscle becomes at the pylorus. After placement of a row of interrupted silk sutures, the remnants of the pouch are cut away, leaving only enough tissue to permit easy approximation of the edges, *without inversion*. If the circular muscle of the pouch is particularly well developed, a second row of interrupted silk sutures may be placed, if it is felt desirable. The final approximation of the edges of the peritoneal muscular cuff may be made with running catgut or a few silk sutures. As a final gesture, the closed pouch is covered with a wisp of omentum or it may be buried

gently in the extreme right portion of the right transverse mesocolon. Drainage is not employed.

Ordinarily, patients in our clinic are dismissed from the hospital on the eleventh day after gastric resection. In this latter group of antral exclusion operations, only one patient stayed longer. This patient developed a prostatitis from an indwelling urethral catheter (the only complication in the series), necessitating a postoperative hospital stay of twenty days.

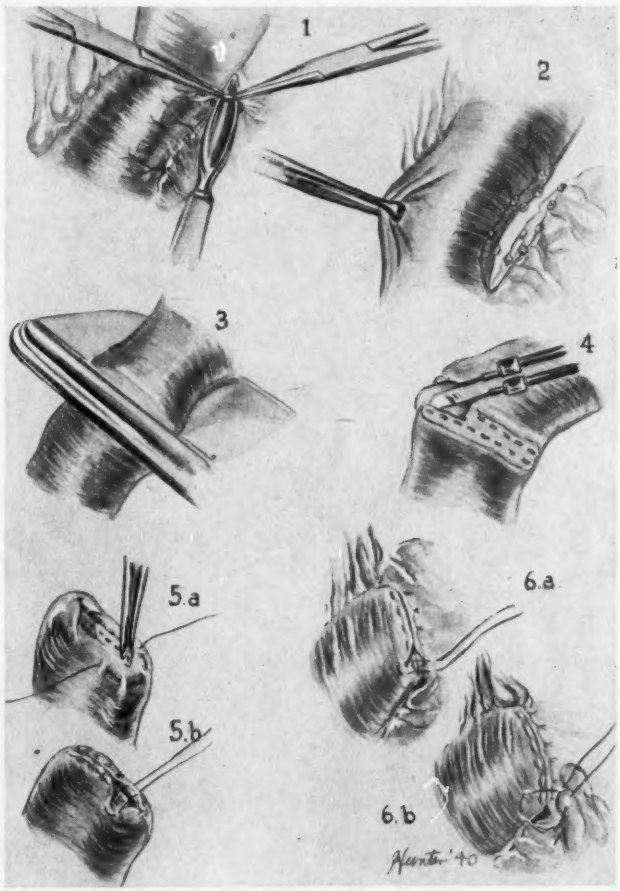

Fig. 5A.

Fig. 5.—*A* and *B*, Methods in use in this clinic for performance of the Group 3 operation in which antrum and pylorus are excised. *A*, The method of election for closure of the duodenum; *1* to *6* indicate the various steps in the procedure. (Reproduced from SURGERY 8: 275, 1940 and Surg., Gynec. & Obst. 72: 260, 1941.)

INDICATIONS FOR THE ANTRAL EXCLUSION OPERATION

The only justification for this procedure lies in the rather frequent occurrence of an indurated duodenal ulcer; under these circumstances it is difficult to mobilize the duodenum and obtain a secure closure. During the past year, it has been observed in this clinic that such ulcers have not infrequently an antecedent story of obstruction. From our

experience it would appear that an occult, sealed duodenal perforation is the most common cause of pyloric obstruction by duodenal ulcer.[20] Duodenal stenosis, in our experience, is a rather uncommon occurrence. An ulcer in the pyloric valve may cause obstruction without actual penetration of the entire wall. This occurrence too, however, is far less commonly a cause of obstruction than the sealed occult duodenal perforation. The area of induration in juxtaposition to the ulcer crater apparently brings about extrinsic duodenal compression and obstruction.

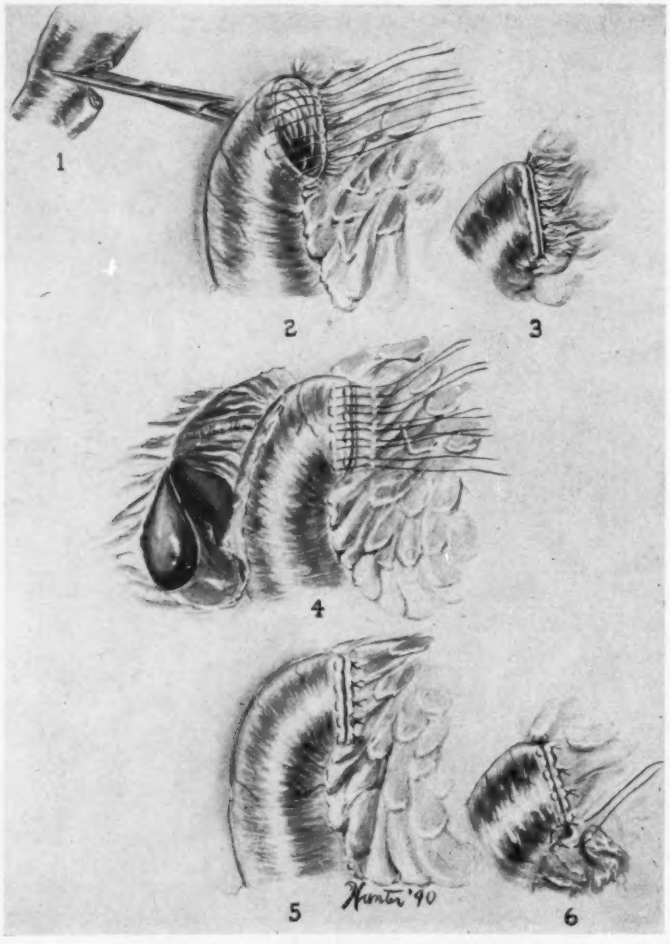

Fig. 5*B*.

Fig. 5*B*.—The method employed for a sealed posterior duodenal perforation in the presence of active hemorrhage, or when the perforation is broken into during the course of the dissection.

It is this type of case in which the antral exclusion operation is indicated. Whereas a posterior duodenal perforation may be dealt with ordinarily with no great difficulty by the technique shown in Fig. 5*B*, a sealed duodenal perforation at the superior margin of the duodenum (at the gastroduodeno hepatic ligament) is usually very difficult to close effectively by any means (Fig. 6). The area of induration in juxta-

position to the ulcer crater robs the surgeon of readily available tissue to utilize in the closure. Yet, even these ulcers may be closed when the surgeon encounters this situation in an actively bleeding duodenal ulcer; under these circumstances he is forced to uncover the bleeding point. In the patient, with a bleeding duodenal ulcer, operated upon after the risk of active hemorrhage has passed, the antral exclusion operation may be considered to be the operative procedure of choice. If the surgeon fails to suppress his curiosity over the nature of the ulcer crater and pursues his dissection until he ascertains its exact nature, he may become ensnared in a trap by the supraduodenal ulcer perforation. This meddlesome venturesomeness of the surgeon may cost him hours of tedious effort to extricate himself and his patient from the difficulty. It is for this type of duodenal ulcer that the antral exclusion operation is ideal. It saves the surgeon much labor and grief.

Obviously, the antral exclusion operation is not intended for a perforated prepyloric ulcer. In order to insure maximal protection against ulcer recurrence, *all* of the antral mucosa *must* be excised.

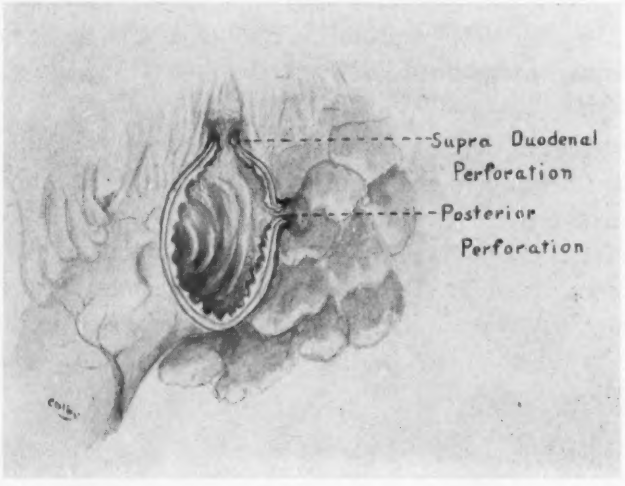

Fig. 6.—Schematic drawing illustrating the common sites of sealed perforation which give rise to the necessity of performing the antral exclusion operation with excision of antral mucosa; it is the supraduodenal perforation which is particularly difficult to close and for which the operation described herein is particularly adapted.

Allen and Welch (1942) state that "McKittrick has suggested a deliberate two-stage resection in poor risk patients who have extensive ulceration or inflammatory reaction." Finsterer (1940), too, employs the two-stage antral exclusion operation in patients who have both duodenal ulcer and cholelithiasis. In this clinic, the one-stage gastric resection is done regularly, the patient, if obstructed, being prepared by intragastric drip feedings of a mixture rich in carbohydrate and protein and low in fat (Varco, gastric diet No. 2),[17] or by intravenous feedings if the pyloric obstruction does not relent. Simultaneous excision of a diseased gall bladder encountered coincidentally during gas-

tric resection for ulcer or carcinoma has been performed a number of times in this clinic. As yet, no suggestion has been observed that such an additional procedure enhances the risk. Obviously, the surgeon must be willing to take enough time to do the incidental procedure as well as the one for which operation was undertaken primarily. Our practice has been to attempt to prepare the patient well for *one* operation and to take enough time to do it to the surgeon's complete satisfaction. The experience of this clinic suggests definitely that the necessity of operating quickly is only a myth, granted satisfactory preoperative preparation of the patient and well-controlled management of the patient during and after operation.

SUMMARY AND CONCLUSIONS

The success of the antral exclusion operation when combined with simultaneous extensive gastric resection suggests that: (1) The pyloric sphincter need not be excised to effect a cure of ulcer; (2) the duodenal ulcer may be left and the ulcer diathesis done away with; it is not the ulcer itself which constitutes the real hazard for the patient with an ulcer, but the acid ulcer diathesis. Extensive gastric resection, when accompanied by complete excision of the antral mucosa, abolishes the ulcer diathesis.

The antral exclusion operation with sacrifice of all of the antral mucosa when accompanied by an extensive gastric resection is a satisfactory and effective operation for so-called irremovable or inoperable duodenal ulcer. The operation has not come into general favor among gastric surgeons because of the likelihood of leakage from the residual antral pocket. A technique of performing the antral exclusion operation, with excision of the antral mucosa in which leakage can be avoided, is described.

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OPERATIVE TECHNIQUE FOR INTRATHORACIC GOITER WITH ESPECIAL REFERENCE TO THE MAINTENANCE OF AN AIRWAY

WILLIAM H. PRIOLEAU, M.D., F.A.C.S., CHARLESTON, S. C.
(From the Department of Surgery, Medical College of the State of South Carolina)

ONE of the chief difficulties in the removal of an intrathoracic goiter is the maintenance of an adequate airway. While an intratracheal catheter inserted immediately before the operation accomplishes this, its use is attended by certain difficulties and dangers. Its introduction may be hindered by such conditions as displacement of the larynx, spasm of the vocal cords, and narrowing and angulation of the trachea. Extension of the neck for the purpose of passing the catheter may not be tolerated by the patient because of obstruction to breathing. These difficulties may be overcome in part by local anesthesia of the larynx and a skillful anesthetist.

In the presence of tracheal obstruction, general anesthesia cannot be relied upon for the introduction of the catheter. Inhalation anesthesia may provoke spasm of the larynx. Also, a sufficient amount of the anesthetic agent may not pass the partially obstructed trachea. Rectal or intravenous anesthesia would avoid the foregoing objections, but still are not suitable, as patients with an inadequate airway do not maintain a sufficient air exchange under general anesthesia, a conscious effort apparently being necessary. Contrary to the above, Lahey[3] reports that sufficient depth of anesthesia and relaxation for the passage of the intratracheal catheter generally can be obtained by inhalation of a mixture of oxygen, cyclopropane, and helium. Helium, due to its low specific gravity, acts as a diluent of the oxygen and permits it to pass more readily by the obstruction. Sise[4] later reports this to be effective in only the mildest cases of obstruction.

Regardless of the anesthesia employed, an unsuccessful attempt to insert an intratracheal catheter may result in a complete obstruction to respiration, necessitating a tracheotomy under most adverse conditions. If an intratracheal catheter is decided upon, it would appear safer to make a preliminary exposure of the trachea under local anesthesia, a procedure in itself not without difficulty in the presence of considerable overlying thyroid tissue.

While an intratracheal catheter protects the trachea against collapse by operative manipulation and thus facilitates the removal of the gland, its passage and presence may be attended by some trauma to the larynx

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and trachea. Postoperative tracheitis and edema of the larynx causing obstruction may be the likely consequences. When the trachea is very thin, it is difficult to see why perforation may not occur, though I have found no reported case.

Few intrathoracic goiters require the use of an intratracheal catheter for their removal. The decision as to its necessity generally cannot be made prior to operation. In the presence of tracheal obstruction local anesthesia alone should be used at least until the trachea has been exposed. After exposure of the trachea, should an intratracheal catheter be considered necessary, it may be inserted through a tracheotomy and the operation continued under local or general anesthesia, or the catheter may be passed transorally in which case general anesthesia would be instituted. The technique of the removal of an intrathoracic goiter is materially affected by whether or not an intratracheal catheter is used. Without a catheter in place, local anesthesia is generally used. Extreme gentleness is of the utmost importance. Operative manipulation must guard against increased pressure upon the trachea and, if possible, steadily relieve the pressure already upon it. In case the obstruction is at the superior strait, the airway often improves sufficiently during the course of the operation to permit the institution of inhalation anesthesia. The use of the intratracheal catheter is usually attended by general anesthesia, particularly if the transoral route is used. The trachea is protected against obstruction and the patient is unconscious of pain, thus permitting a more rapid performance of the operation.

It is my practice to use the intratracheal catheter not as a routine procedure of choice but only when indications for its need develop during the course of the operation. The catheter is then passed through a tracheotomy tube. The management of these cases in this manner will be considered.

Absolutely essential is proper preoperative preparation. Upon admission to the hospital these patients often maintain an adequate air exchange only with a conscious effort. Sleep brought on by exhaustion is soon interrupted by periods of respiratory obstruction likely caused by change in the position of the head. Coughing paroxysms are frequent and often appear alarming. They are generally caused by attempts to bring up accumulations of mucus that may collect below the obstruction. One patient was observed to bring up long casts of the trachea and bronchi, which she would extract with her fingers.

In most instances the pressure symptoms are greatly relieved by bed rest and the use of opiates and other sedatives. The cough practically subsides, the excess mucus ceases to form and breathing becomes easier. Hyperthyroidism, if present, must be taken into proper account. The usual preoperative treatment requires from one to several weeks.

The position of the patient on the operating table must be such as to permit an adequate air exchange, without undue effort. This is often

an awkward position for the performance of the operation. Particular care must be taken not to excite the patient or cause undue pain, as struggling caused thereby will result in exhaustion and likely complete respiratory obstruction necessitating a tracheotomy under most unfavorable conditions.

Novocain is infiltrated into the operative field, first subcutaneously and then as the operation proceeds. A long horizontal incision is made through the skin and platysma a few centimeters above the clavicles. Upper and lower flaps are reflected. The prethyroid muscles are divided in the midline from the thyroid cartilage to the sternum and then divided transversely on one or both sides as indicated.

Bleeding points must be ligated as encountered so as not to place the weight of the instruments upon the trachea and also to keep the operative field clear in case a tracheotomy becomes necessary. All manipulations must avoid pressure upon the trachea.

The trachea should now be well exposed. This may be done by proceeding between lobes or nodules. Often it is necessary to divide the overlying thyroid tissue. Once the trachea has been exposed the operator feels that he has control of the situation as he can safely make an opening for the insertion of a tube in case of obstruction to breathing. Before this a tracheotomy can be performed only with difficulty and danger, due to almost uncontrollable bleeding in a patient struggling for air. Should general anesthesia be necessary, only now can it be instituted without undue risk, particularly is this the case in the presence of obstruction.

The operation now proceeds along lines of least resistance freeing the upper pole, the lateral veins, and the tracheal attachments in order of easiest approach. It is important that all cervical attachments[1, 2] be severed before attempting to deliver the mass from within the thorax. The one exception is the inferior thyroid artery which generally cannot be exposed without manipulating the gland so as to obstruct the trachea. The lobe is then firmly grasped with forceps, freed from its thoracic attachments by finger dissection, and delivered. During the act of delivery there may be obstruction of the trachea which is permissible for only a few seconds at a time. The lower pole is now cared for in the usual manner with due care to avoid injury to the recurrent laryngeal nerve. The preliminary removal of the contralateral cervical lobe is sometimes of advantage in affording more room. Drainage is generally advisable due to the tendency of fluid to collect in the space from which the goiter has been removed.

A lobe too large to be delivered intact may often be successfully removed by incising[3] its capsule and breaking down its contents with the finger, thus reducing its size. An intrathoracic goiter occasionally is of such size, position, and fixation that it cannot be removed through an intact superior strait. In such cases a mediastinotomy becomes necessary. The cervical approach is made as described. A counter incision

is made over the midsternum. The sternum is bisected to the second or third interspace at which level it is divided to the indicated side and the incision continued in the intercostal space. This results in the formation of a sternoclavicular costal flap which can be retracted anterolaterally, greatly enlarging the superior strait. Even with this exposure, delivery of the goiter may be difficult if it is situated posteriorly to the large blood vessels. In such an operation local anesthesia ceases to be adequate beyond the cervical portion, particularly for the retraction of the chest wall flap; however, by this time there is generally sufficient airway to permit an inhalation anesthesia. Otherwise anesthesia can be administered through an intratracheal catheter passed through a cervical tracheotomy. This operation is followed by considerable pain in the shoulder and upper costovertebral region. Partial removal of the sternum by rongeur is held preferable by some.

Should a tracheotomy be necessary the tube should be inserted low through a horizontal incision between two rings. If no longer necessary at the end of the operation, the tube can be removed and the opening closed with pretracheal fascia.

By following this plan of management, unnecessary trauma to the trachea and the larynx by the inlying catheter is avoided by limiting its use to those cases in which it is necessary for the maintenance of an adequate airway. There is provided the safety factor of exposure of the trachea as a preliminary procedure in case intratracheal catheterization should become necessary. As the operation proceeds there is the tendency for a steady increase in the size of the airway except for the period during the delivery of the intrathoracic lobe. The constant care necessary to avoid pressure upon the trachea and the use of local anesthesia prolong the operation and make it more exacting upon the surgeon, but also add to its safety. The use of the intratracheal catheter during operation can be avoided to advantage in most cases of intrathoracic goiter and in nearly every case of tracheal obstruction due to external pressure in the neck, such as cervical goiter, malignancy, and abscess.

CASE 1 (Hospital No. 29459).—J. W. S., a white woman, aged 34 years, was admitted to the Roper Hospital, Oct. 14, 1938. She had first noticed the presence of a goiter four or five years previously. She had been advised by a physician that treatment was unnecessary as the basal metabolic rate was not elevated. During the past nine months the goiter had increased in size and she had symptoms from pressure upon the trachea. She complained of palpitation, nervousness, and emotional instability and had lost twenty pounds in weight.

The positive physical findings were nervousness, a staring expression, and tachycardia, all of a moderate degree. On both sides and in front of the trachea there was a large, firm, nodular mass of thyroid gland, extending well posteriorly and inferiorly. The basal metabolic rate was minus 11 per cent and the blood cholesterol 163 mg. per cent. X-ray examination showed a well-defined area of increased density extending several centimeters to the right of the trachea and situated well below the superior strait (Fig. 1).

The diagnosis was nodular goiter, cervical and intrathoracic with partial obstruction of the trachea, and mild hyperthyroidism.

On Oct. 21, 1938, operation was performed. Anesthesia was obtained by local infiltration of novocain. A low collar incision was made through the skin and flaps were reflected. A midline incision was made between the prethyroid muscles to the thyroid gland. The isthmus was divided and the trachea was exposed. A subtotal resection of the left lobe was made by freeing first the tracheal attachments, then the upper pole, the lateral veins, and finally the lower pole which extended well beneath the clavicle. The cervical portion of the right lobe was resected in a similar manner, being severed from the intrathoracic portion to which it was only slightly attached. The intrathoracic mass was grasped with forceps and freed by finger dissection; its size prevented its delivery. Its capsule was then incised and the contents broken down by digital manipulation, following which it was easily delivered and removed. A rubber tissue drain was placed on each side of the trachea and the wound was loosely closed. Thirty hours after operation there developed breathing difficulty and a fullness of the operative region. A deep hemorrhage was suspected and, accordingly, the wound was opened. A large blood clot was found to the right of the trachea. There was some oozing of bright red blood from the right lower pole, but no definite bleeding point was located. The wound was packed loosely with gauze. It was closed with drainage in twenty-four hours. The convalescence otherwise was smooth.

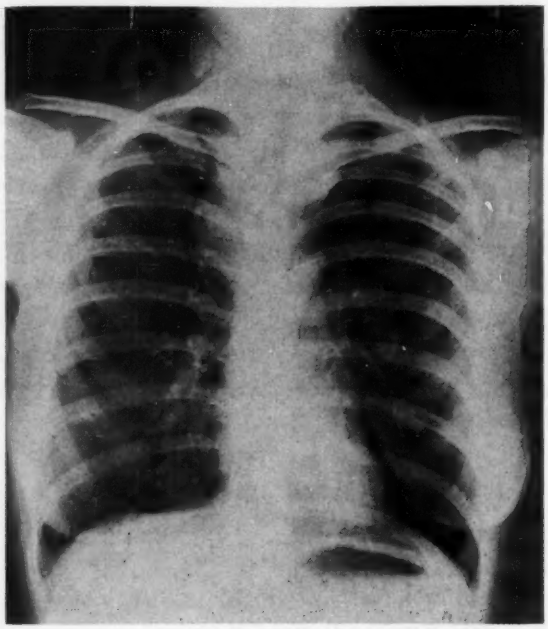

Fig. 1 (Case 1, J.W.S.).—Intrathoracic goiter before operation.

Pathologic Report.—The specimen consisted of three masses of nodular thyroid tissue, the largest being 6 by 5 by 2½ cm. Section revealed numerous nodular and cystic structures. Microscopic examination showed that in places the follicles were of various sizes, lined with flattened cuboidal cells, distended with colloid, and surrounded by dense hyaline connective tissue trabeculae. Some of the larger follicles showed hyperplasia of the lining epithelium with formation of papillary buds and resorption of colloid. There were a few areas of empty follicles and nests of epithelial cells.

In September, 1939, the patient was enjoying good health. She no longer had symptoms of pressure upon the trachea. She appeared to have a normal thyroid balance. There was no palpable thyroid tissue in the neck.

CASE 2 (Hospital No. 31948).—J. T. H., a white woman, aged 55 years, was admitted to the Roper Hospital, Feb. 11, 1940. She had known of the presence of a goiter since the age of 16 years. There had been a gradual increase in its size. Lately she had been conscious of pressure in her neck causing difficulty in breathing, which was very pronounced at times. She had attacks of strangling in her sleep.

Physical examination revealed a large nodular mass of thyroid tissue on each side of the trachea, the right being larger than the left. The basal metabolic rate was plus 12 per cent, the blood cholesterol 167 mg. per cent. X-ray examination showed a moderate widening of the upper mediastinum which overshadowed most of the apex of the lung on each side (Fig. 2).

The diagnosis was nodular cervical and intrathoracic goiter with partial obstruction of the trachea.

Fig. 2 (Case 2, J.T.H.).—Intrathoracic goiter before operation.

On Feb. 15, 1940, operation was performed under local infiltration of novocain. A low collar incision was made through the skin. Flaps were reflected. An incision was made between the prethyroid muscles to the thyroid gland. Dissection was carried between the right lobe and the isthmus so as to expose the trachea. The isthmus was removed. The right lobe was the more accessible and thus resected first. This was done by freeing the tracheal attachments, the upper pole, and the lateral veins. The intrathoracic portion was then easily delivered and the lower pole severed. As the left lobe was much larger and of difficult approach, the prethyroid muscles were divided transversely. The trachea and larynx were displaced far to the right. The left lobe was mobilized by severing the tracheal attachments, the upper pole, and the lateral veins, in the order named. The intrathoracic portion was freed by finger dissection and then delivered with some difficulty, causing momentary obstruction to the trachea. The lower pole was severed and the lobe resected, leaving a small strip of tissue posteriorly. Black silk was used for hemostasis. A rubber tissue drain was placed on each side of the trachea and the wound closed. The convalescence was uneventful.

Pathologic Report.—The specimen consisted of two nodular masses of thyroid gland with a combined weight of 125 Gm. On section the tissue was reddish brown and showed circumscribed areas of cystic degeneration, colloid accumulation, and

partial calcification. Microscopic examination showed nodular areas of thyroid tissue with large cystic acini lined by flattened epithelium and containing well-staining colloid. In areas the stroma was hyaline. There were some areas of closely packed acini with cuboidal lining cells. There was some evidence of old hemorrhage and calcification.

On June 11, 1940, the patient was enjoying good health. There was no palpable thyroid tissue in the neck. She appeared to be in a state of normal thyroid balance.

CASE 3 (Hospital No. 22233).—W. H. L., a white woman, aged 51 years, was admitted to the Roper Hospital on June 7, 1934. She had a long history of bronchitis, hay fever, and asthma. Palpitation of the heart had existed for some years. Lately she had been very nervous and had swelling of the ankles. For the previous two months, she had had coughing spells of such severity that she found it difficult to catch her breath. Often she coughed up long plugs of mucus which she had to extract from her throat with her fingers, following which she felt relieved. Her temperature was elevated at times. There had been a recent loss of weight.

Fig. 2 (Case 3, W.H.L.).—Intrathoracic goiter before operation.

Physical examination showed a thin, nervous woman with a pulse of 120, and blood pressure of 135/85. There was a moderate-sized nodular enlargement of the thyroid gland on each side of the trachea. X-ray examination revealed a well-defined widening of increased density on each side of the sternum, of greater degree on the right than on the left. The trachea was considerably narrowed at the level of the superior strait and below (Fig. 3).

The diagnosis was nodular goiter, cervical and intrathoracic, with partial obstruction of the trachea. During the preoperative hospital stay of two weeks, the cough practically subsided and the general condition of the patient improved greatly.

On June 20, 1934, operation was performed under local infiltration of novocain. A collar incision was made through the skin and flaps were reflected. A midline incision was made between the prethyroid muscles to the thyroid gland. The trachea,

which was far posterior, was exposed by bisecting the overlying thyroid tissue. The cervical portion of the right lobe was then mobilized by severing the tracheal attachments, the upper pole, and the lateral veins. The intrathoracic portion was then freed by finger dissection. Its delivery was difficult, necessitating compression of the trachea. Resection was then performed leaving a small strip of thyroid tissue posteriorly. A light nitrous oxide oxygen anesthesia was administered during the delivery of the intrathoracic lobe. At times it appeared as if a tracheotomy with an intratracheal catheter might be necessary. Limited exploration to the left of the trachea revealed a small nodular mass which it was deemed advisable not to resect on account of the difficulty of the operation thus far. Plain catgut was used for hemostasis. A cigarette drain and a small rubber catheter were placed to the right of the trachea and the wound closed. Except for mild shock after the operation, the convalescence was smooth.

Pathologic Report.—The specimen consisted of a large mass of lobulated red tissue. Microscopic examination revealed the acini of various sizes and distended with colloid. There was considerable lobulating fibrosis. In some areas there were lymphoid collections and epithelial hyperplasia.

On July 16, 1934, a routine x-ray examination showed a moderate widening of the upper mediastinum with a well-defined area of density extending to the right. In spite of its being on the right, it was interpreted as an intrathoracic nodule arising from the left lobe (Fig. 4).

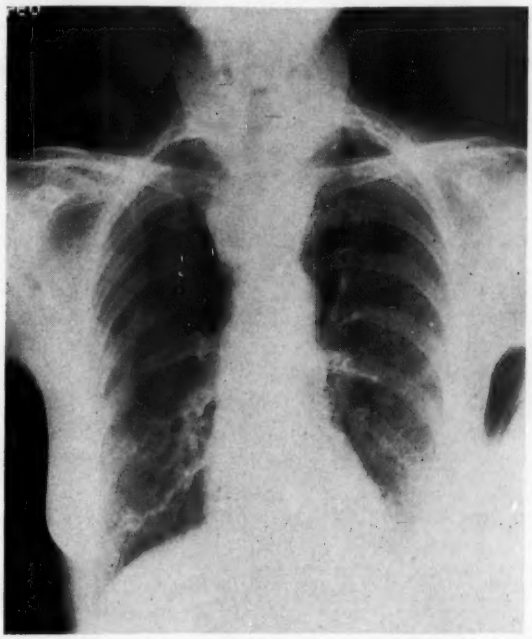

Fig. 4 (Case 3, W.H.L.).—July 16, 1934, tumor mass to right of trachea twenty days after removal of intrathoracic lobe on same side; this mass apparently arose from the left side.

On Sept. 20, 1934, the patient was enjoying good health and had no cough. In December, 1934, she had an upper respiratory infection with a severe cough. Removal of the remaining intrathoracic mass was advised. In April, 1936, the patient had an illness characterized by a severe cough and fever.

On Feb. 21, 1941, she again came under observation. She was having severe coughing spells, nervousness, and palpitation of the heart. X-ray examination showed that the mass noted in July, 1934, had doubled in size. She still did not consent to having it removed (Fig. 5).

COMMENT

In Cases 1 and 2, preliminary removal of the contralateral lobe facilitated the removal of the intrathoracic lobe. In Cases 1 and 3, incision of the capsule resulted in such reduction in size as to make delivery possible. In all three cases, while delivery of the intrathoracic lobe was attended by momentary obstruction of the trachea, in no case was an intratracheal catheter necessary.

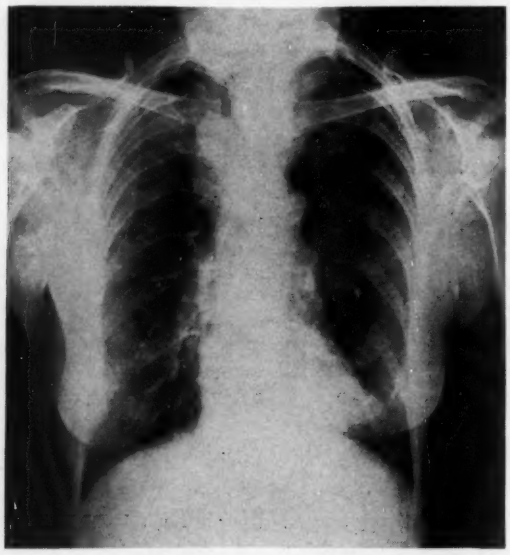

Fig. 5 (Case 3, W.H.L.).—Feb. 21, 1941, tumor mass has increased greatly in size.

CASE 4 (Hospital No. 32310).—K. L. A., a white woman, 47 years of age, was admitted to the Roper Hospital, April 16, 1940. In June, 1929, she had had (by W. H. P.), at another hospital, a conservative subtotal thyroidectomy for a large nodular colloid goiter involving both lateral lobes and the isthmus, and extending beneath the clavicles on both sides. The pathologic report is not available. The result of the operation was relief for a number of years from the pressure symptoms of which the patient complained. A mild hyperthyroidism was also relieved.

In July, 1930, she complained of a sore throat and a feeling of fullness in her chest. In October, 1934, she stated that she was in good health. Examination revealed the larynx slightly displaced to the left.

The patient again came under observation in April, 1940. Since an attack of influenza two months previously, she had noticed increased breathing difficulty with frequent paroxysms of coughing. She complained also of dysphagia, epigastric distress, and soreness in the right chest. She had become nervous and had lost seven pounds. She brought with her an x-ray film showing the presence of a large, well-defined dense homogenous mass occupying the right upper thorax. The trachea was displaced to the left. Examination of the neck revealed no palpable thyroid tissue. The vocal cords functioned normally. A diagnosis of intrathoracic goiter was made and operation was advised (Fig. 6).

On April 22, 1940, operation was performed. General anesthesia was instituted at the start, inasmuch as the trachea was easily accessible as a result of the previous thyroidectomy; there was no tracheal obstruction demonstrable at the time of operation, and a superior mediastinotomy was going to be necessary. The usual

thyroid approach was made. The trachea was well exposed and the prethyroid muscles on the right divided transversely. There was a small strip of thyroid tissue to the right of the trachea; it had no connection with the intrathoracic mass. With this exposure the intrathoracic mass could not be located, nor could the finger be passed into the thorax. The sternum was bisected for 6 cm. and a flap formed including a portion of the sternum, the clavicle, and the first two ribs. Upon retraction of this flap the intrathoracic mass was readily recognized. It was fixed with forceps and freed anterolaterally by finger dissection. The inferior border could not be reached, the posterosuperior portion was firmly adherent. Being too large to deliver, the capsule was incised and the contents broken down by finger dissection. Delivery was accomplished, but with difficulty, due to the anteriorly placed subclavian artery. The posterosuperior portion was freed with some difficulty from the apex of the thoracic cavity. A nerve firmly adherent to the mass was recognized and unavoidably severed. It was thought to be the phrenic nerve but later proved to be recurrent laryngeal. Fine chromic catgut was used for hemostasis and closure of the muscle layers, alloy steel wire for the sternum, and clips for the

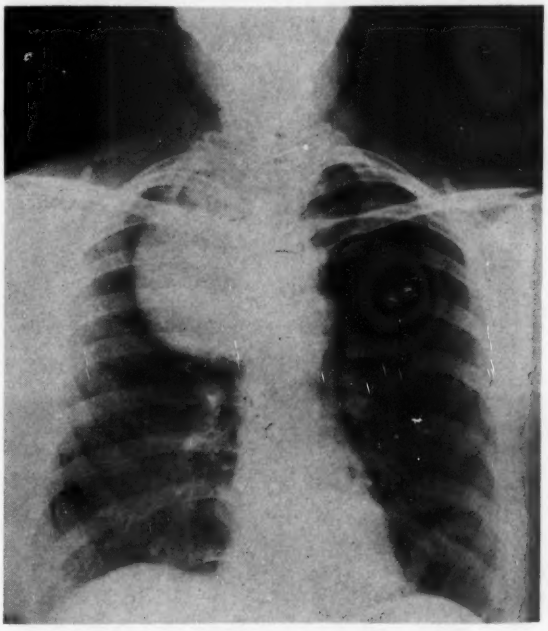

Fig. 6 (Case 4, K.L.A.).—Large, wholly intrathoracic goiter on right, March 4, 1940.

skin. A large rubber tissue drain was inserted into the space formerly occupied by the goiter and brought out through the neck incision. The operation required two hours. Following the operation the patient was in a moderate degree of shock. Otherwise the convalescence was satisfactory. She left the hospital on the twelfth day after the operation. There was a paralysis of the right vocal cord which has persisted to date (Fig. 7).

Pathologic Report.—The specimen consisted of an oval slender nodular mass 11 by 7 by 4 cm. On section the tissue was irregularly fibrotic and partially calcified. There was a stringlike slender piece of fibrous tissue 9 cm. in length. Microscopic examination showed irregularly distended follicles filled with colloid showing areas of cystic degeneration and fibrosis. A slender strip of fibrous connective tissue and fat contained minute imbedded nerve filaments.

On Oct. 10, 1940, she had the appearance of a normal thyroid balance. The incision was firmly healed. She complained of pain in the right shoulder and upper

right dorsal spine and numbness and tingling of the right hand. Chvostek's sign was positive. Calcium and cod-liver oil were prescribed.

On June 15, 1941, she was nervous. The above symptoms were more pronounced. X-ray examination of chest, shoulder, and spine was negative (Fig. 8). Diagnosis was parathyroid tetany.

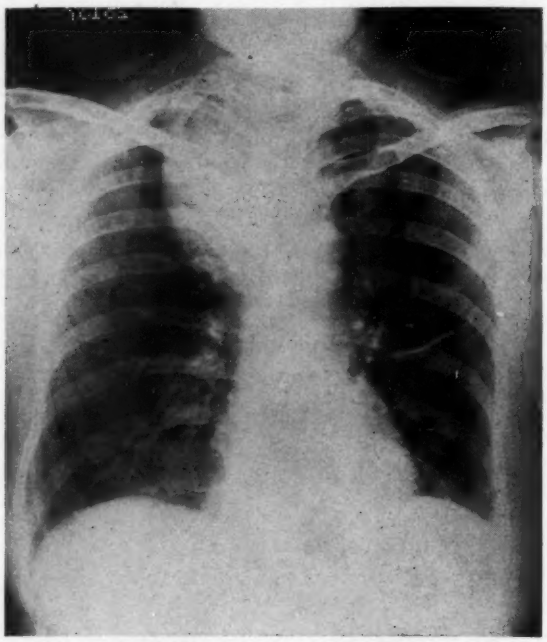

Fig. 7 (Case 4, K.L.A.).—Ten days after the removal of intrathoracic goiter.

Fig. 8 (Case 4, K.L.A.).—June 14, 1941, one year after the removal of the intrathoracic goiter.

On July 17, 1941, the blood calcium was 8.6 mg., phosphorus 2.98 mg. Dihydrotachysterol, 1 c.c., twice a week, and calcium and cod-liver oil were prescribed.

On Aug. 25, 1941, the blood calcium was 7.8 mg., phosphorus 4.03 mg. She had improved to some extent. The dihydrotachysterol was increased to 1 c.c. three times a week.

On Sept. 26, 1941, the blood calcium was 8.7 mg., phosphorus 3.52 mg. The symptoms of tetany had practically subsided. The dihydrotachysterol was increased to 1 c.c., six times a week.

On Nov. 7, 1941, the symptoms of tetany had subsided. Blood calcium was 10.6 mg., phosphorus 4.62 mg. Dihydrotachysterol, 10 mm. daily, was prescribed, also calcium gluconate, 3 Gm. daily.

COMMENT

This patient had an unusually large completely intrathoracic goiter. It was larger than reported by the pathologist as it was reduced in size so as to permit its delivery. Whether it arose from a nodule overlooked at the previous thyroidectomy or from an aberrant rest cannot be determined. A similar case of Allen's was reported by Means.[2] A mediastinotomy was necessary for the removal of the tumor. An obstacle to delivery was the anteromedially situated subclavicular artery. An adequate airway was maintained without an intratracheal catheter.

SUMMARY

1. In the removal of an intrathoracic goiter the use of the intratracheal catheter has its disadvantages as well as its advantages; it is generally unnecessary.

2. The operative technique whereby the use of the intratracheal catheter may be avoided is described.

3. Four cases are reported.

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A NEW THEORY CONCERNING THE ETIOLOGY OF RIEDEL'S STRUMA

JOSEPH L. DE COURCY, M.D., CINCINNATI, OHIO
(From the Department of Surgery, De Courcy Clinic)

ALTHOUGH ligneous or woody thyroiditis was described as a specific entity by Riedel in 1896, the etiology of this syndrome is still obscure. My object in presenting this paper is an attempt to explain a new etiology of Riedel's struma. I feel that this disease is the result of a previous perithyroiditis which causes a partial constriction of the vessels entering the gland.

As a disease of the thyroid, Riedel's struma is a relatively rare occurrence. Both sexes are about equally affected, generally during the fourth decade of life. However, the condition may appear in younger or in much older individuals. This condition has occurred in the De Courcy Clinic in about 2 per cent of all thyroidectomies and its incidence appears to be about the same as that of cancer of the thyroid.

In woody thyroiditis, the thyroid is enlarged, smooth, and with a characteristic stony hardness or, as Riedel has described it, "iron hardness." As a rule, the disease involves first one lobe and then the other. Pathologic changes which occur result in gradual conversion of the gland into fibrous tissue through which scattered atrophic acini may be found. In many cases, fixation of the gland to the surrounding tissues takes place and the adherent tissue makes surgery difficult.

SYMPTOMATOLOGY AND DIAGNOSIS

Toxic symptoms are generally entirely absent in the early stages. The basal metabolic rate may be normal. However, as a result of the connective fibrous infiltration and the gradual enlargement of the gland, which causes compression upon the trachea, esophagus, and larynx as well as on the neighboring nerves and blood vessels, more definite symptoms begin to be manifest. Dyspnea and dysphagia are the first signs. The feeling of pressure is usually followed or accompanied by hoarseness, stridor, or even aphonia, due to involvement of the laryngeal nerves.

From a review of the literature, one would judge that the onset of Riedel's struma is not acute. Lee[2] describes its onset as "insidious," while Fox and Missal[3] state that the average duration of symptoms is about seven months. This, however, is not always true. During the past year I have operated upon two patients with Riedel's struma who entered the hospital acutely ill and remained for surgery. I will describe these cases in more detail later in the paper.

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Though admittedly difficult, the diagnosis of woody thyroiditis usually can be made prior to operation by the characteristic consistency of the gland and by a normal or mildly elevated basal metabolic rate. This at once differentiates it from diffuse toxic goiter. Carcinoma of the thyroid should be considered but usually occurs in the presence of an already existing goiter. Although the hardness of the gland suggests carcinoma, the absence of nodules and the indefinite borders of the glandular enlargement help further to differentiate Riedel's disease from cancer.

The disease must also be differentiated from acute suppurative thyroiditis. However, in Riedel's disease a rapid subsidence of the temperature and a tendency to fibrous formation rather than suppuration become evident.

Hashimoto's disease, formerly etiologically associated with Riedel's struma by some authors but now quite generally recognized as a separate syndrome (Hertzler[4]), may likewise readily be differentiated from woody thyroiditis. Chronic lymphoid thyroiditis (Hashimoto) is characterized by diffuse and extensive lymphatic infiltration, while in Riedel's disease the regional lymph nodes remain uninvolved. Though other symptoms are somewhat similar, in Hashimoto's disease the enlargement is bilateral, usually occurs in women over forty, and is less fixed and much less adherent than in fibrous thyroiditis.

THEORIES OF ETIOLOGY

The etiology of Riedel's struma or ligneous thyroiditis is still unknown. However, many theories as to its cause have been advanced. Some have been discarded while others still have their adherents. Specific organisms have not been noted consistently in fibrous thyroiditis. It is generally conceded that syphilis and tuberculosis are probably not the cause of this condition. Actinomyces, streptococci, and other organisms have been practically ruled out as etiologic factors.

Among contemporary authors, there are those who adhere to the view that Riedel's struma is a result of a local inflammatory process in the thyroid. This view was held by Graham,[5] in 1931. He pointed out that in these cases the general body economy is affected only secondarily by reason of the destruction of the thyroid, interference with deglutition, and injuries to important blood vessels and nerves. Such a process, he noted, has its counterpart in other organs and tissues, which may be expected to respond in a similar manner except for the fact that the thyroid is so situated that complications can occur readily.

Much the same view was expressed more recently by Harry.[6] When discussing the pathogenesis of Riedel's disease, it was his opinion that the evidence suggests the process to be chronic inflammatory in nature. In keeping with this view, he cited such factors as the early stimulation of the gland function, followed by destruction of the parenchyma, ex-

tensive fibrosis, the presence of cells usually found in chronic inflammatory states, and the presence of similar lesions in the adjacent cervical tissues.

A somewhat modified concept has been presented by McKnight.[7] Remarking that we are prone to forget the fact that inflammatory reactions can be brought about by causes other than bacterial invasion, he suggested that the pathologic picture of Riedel's thyroiditis is due to some as yet obscure biochemical irritant differing from that produced in or causing exophthalmic goiter.

More recently, in describing a case of Riedel's struma in a 33-year-old woman, Zelle and his associates[8] expressed the belief that the disease was caused by abnormal response of the thyroid to physiologic demands.

Conversely, some workers completely doubt the inflammatory nature of the disease. However, there is no convincing evidence to support the view that woody thyroiditis results from adrenal dysfunction or from the degeneration of a previously enlarged thyroid (Harry[6]). Nor is there any satisfactory explanation to be found in embryologic considerations (Zelle and co-workers[8]).

ROLE OF PERITHYROIDITIS

From the foregoing, it would appear that the consensus of opinion up to the present is that Riedel's struma involves the capsule from within and in extreme cases extends far beyond the capsule into the adjacent muscles of the neck. It is my opinion, however, that the true cause is a perithyroiditis and I believe that the fibrous growth begins outside of the gland proper rather than inside the thyroid itself.

That this perithyroiditis always accompanies Riedel's struma in younger persons is demonstrated by the close adherence of the overlying muscles to the gland. It is the purpose of this paper to discuss whether this perithyroiditis is primarily responsible for the woody consistency of the gland or whether it results secondarily from the disease itself.

It has always seemed to me that Riedel's struma is a vascular rather than a glandular disease, one that begins with a perithyroiditis resulting in secondary changes in the gland itself. In this connection, I should like to mention the work of Goldblatt and his associates.[9, 10, 11] In their extensive experimental studies on hypertension, they clearly demonstrated the profound effect of partial occlusion of the renal blood vessels on specific organs and tissues. The fibrous whorls which we find about the blood vessels in Riedel's thyroiditis are very similar to those described by these investigators.

It is possible that the perithyroiditis with the adherent muscles causes a constriction of the thyroid vessels and their superficial tributaries, thus bringing about the fibrous changes which we find in Riedel's disease. Hertzler,[4] in discussing the pathology of this disease, states that the cut surface of the hard, fixed mass is bloodless, the smaller vessels

being compressed by the exudate. Conversely, large vessels may be held patulous by the induration.

In his review of the subject, Harry[6] has noted the variation in the condition of the blood vessels in different specimens of Riedel's struma. He observed that pronounced thickening of the arterioles and small arteries is the rule but that in some cases these vessels appear to be normal. He also noted that the number of capillaries is reduced.

Before going further into a discussion of my views on the etiology of woody thyroiditis, I am going to present briefly two recent cases together with the microscopic findings. These case histories, I feel, will help to clarify my theory.

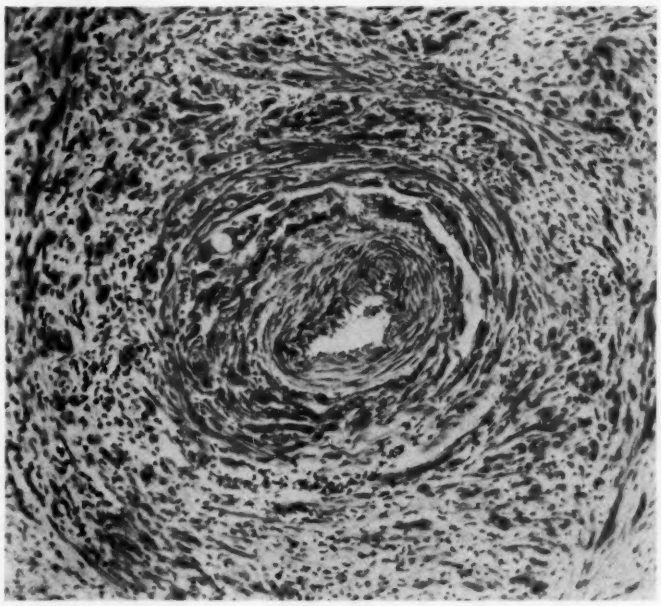

Fig. 1.—A small artery showing hypertrophy of media with reduction of lumen and surrounding collar of dense hyalinized connective tissue; Hortega silver impregnation stain.

CASE REPORTS

CASE 1.—V. P., a 42-year-old white, married female, entered the Clinic on Nov. 8, 1941, because of loss of weight and nervousness. She presented a history of sore throat, which had occurred one month previously but no history of goiter. Her temperature was 102° F.; blood count, 17,800 white cells per c.c.; differential, polymorphonuclears 73 per cent; small lymphocytes, 25 per cent; eosinophiles, 1 per cent; basophiles 1 per cent. Lung fields and heart were normal. Wassermann and Kahn tests were negative.

Her thyroid was symmetrically enlarged, each lobe being about three times normal size. Her neck overlying the gland was exquisitely tender, with no evidence of external inflammation.

She was referred back to her family physician who kept an icebag on her neck and ordered her to remain in bed. Sulfathiazole, 10 gr., was given every four hours for four days. However, because of the persistence of her symptoms, she was admitted to the Good Samaritan Hospital on Nov. 14, 1941.

While in the hospital, her temperature range was between 98° and 102° F. Her pulse was 88; respiration 22; blood pressure, 138/78; basal metabolic rate (two readings), plus 16. No medication was given during this time except Lugol's solu-

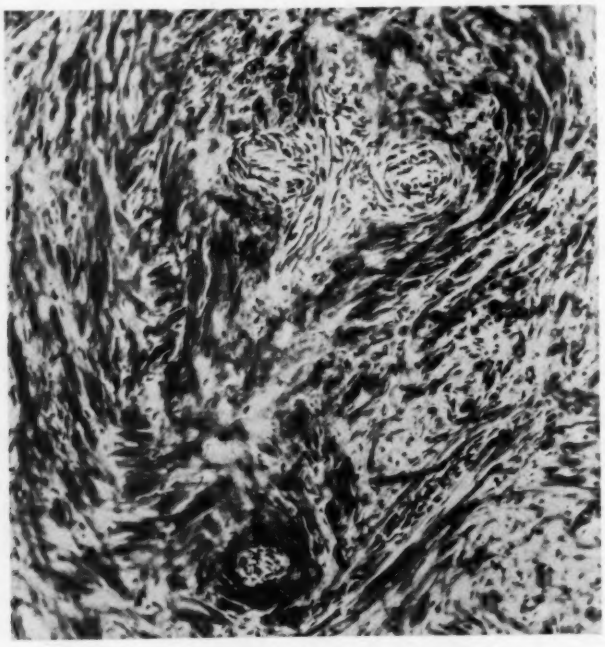

Fig. 2*A*.

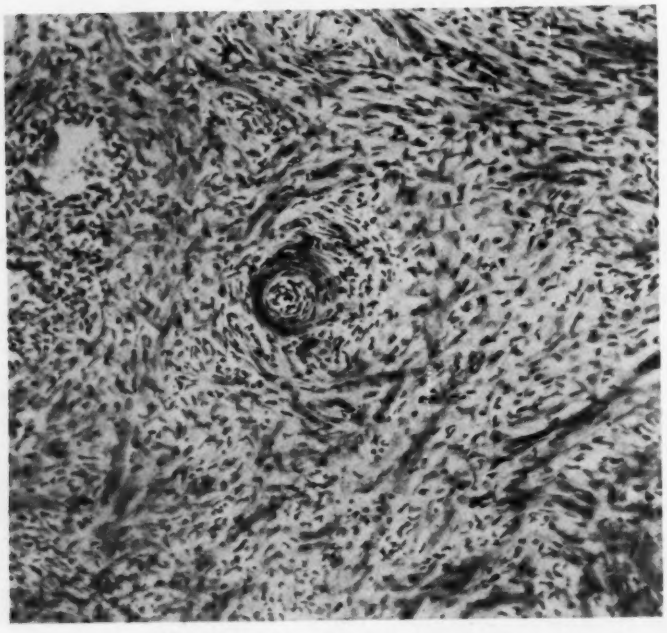

Fig. 2*B*.

Fig. 2.—A small artery showing medial hypertrophy and a precapillary arteriole showing sclerosis, obliteration, and surrounding collar of dense hyalinized connective tissue; marked hyalinization of the entire stroma. (Hortega silver-gold impregnation stain.)

tion. In five days she returned to normal but the thyroid remained enlarged and hard, although the tenderness had disappeared.

Bilateral subtotal thyroidectomy was performed on Nov. 21, 1941.

Examined grossly, the appearance of the excised gland was definitely one of Riedel's struma. The organ was white and muscle fibers in large numbers had densely adhered high over the side of the lobes, which had to be removed by sharp dissection. There was very little bleeding from the cut surfaces. The outer portion of the lobe was most involved and thyroid tissue could be seen beginning about 1 cm. from the capsule. However, the colloid appeared to have a whitish color rather than the red color usually seen.

Dr. William German, pathologist to the Good Samaritan Hospital, reported the following microscopic findings: There was compensatory hyperplasia, intense fibrosis, marked strangulation of functioning thyroid elements, marked arteriosclerosis, formation of pseudogranulomata and pseudogiant cells. The diagnosis was Riedel's struma.

The postoperative period was uneventful. Her temperature reached normal on the fourth postoperative day and remained afebrile at the time of her dismissal.

She has since regained her normal weight and is taking desiccated thyroid, 1 gr. daily, one month after her operation.

CASE 2.—E. K., a 59-year-old, single, white female, entered the Clinic on Sept. 10, 1941. Four weeks prior to admission she had become aware of increasing nervousness, loss of weight, tachycardia, and, at times, a choking sensation in her throat. At the time of admission her temperature was 99° F.; pulse, 88; respiration, 22; blood pressure, 168/90; basal metabolic rate, plus 20. Her thyroid was diffusely enlarged, about two and one-half times normal size, and was quite tender to touch. There was no evidence of external inflammation.

No history of previous goiter could be ascertained, although the patient thought that her neck had appeared to be somewhat swollen over the past four years. However, it had not been as hard as at present. Her blood picture was as follows: hemoglobin, 86 per cent; red blood cells, 4,280,000; white blood cells, 12,800; differential count: polymorphonuclears, 76 per cent, small lymphocytes, 23 per cent, basophiles, 1 per cent. The remainder of the physical examination was essentially negative except for a fine tremor of the hand.

A diagnosis of woody thyroiditis was made and Lugol's solution, 10 drops three times daily, was given.

A subtotal thyroidectomy was performed on Sept. 8, 1941.

The gross pathologic findings in this instance were essentially similar to those found in the previous case; namely, the whitish appearance, the adherent muscles, etc.

The microscopic examination was reported by Dr. William German as follows: There is replacement of thyroid by diffuse struma fibrosa in which there is extensive strangulation of gland-bearing tissue, advanced fibrosis, islands of lymphoid tissue, and formation of pseudogranulomata and pseudogiant cells. There is also marked arteriolar sclerosis. The diagnosis: Riedel's struma.

Forty-eight hours after operation, the patient's temperature became normal and remained so at the time of dismissal on the fifth postoperative day.

DISCUSSION

These cases are interesting because of their acute onset, evidently associated with a perithyroiditis, the tenderness of the overlying structures, and the elevated temperature which subsided quickly with no tendency to suppuration. Of course, one might say that these febrile periods were only exacerbations of an already existing condition. How-

ever, both women were sufficiently intelligent to consult a physician immediately and they would certainly have noticed a hardness in the neck had it existed previously.

It is my opinion that if these patients had not been operated upon, the cases would probably have been classified as acute nonsuppurating

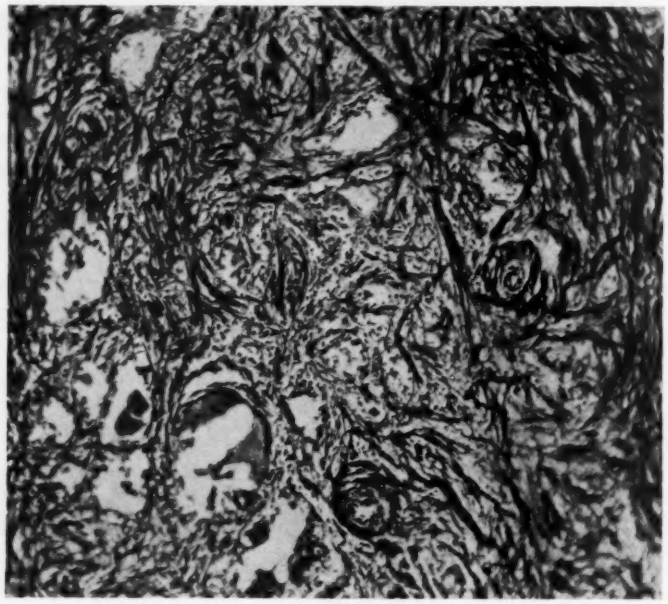

Fig. 3*A*.

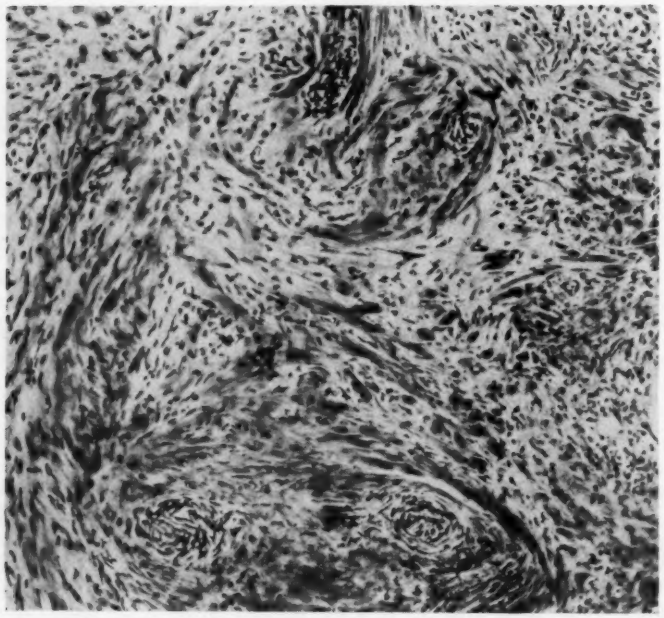

Fig. 3*B*.

Fig. 3.—Photomicrograph showing sclerosed arterioles and obliteration of thyroid acini by fibrous tissue; Hortega double silver-gold impregnation stain.

thyroiditis. Possibly several years would have elapsed before surgery was undertaken and a definite diagnosis made.

It is pertinent that Hertzler,[4] in discussing Riedel's struma, stated that "whatever the disease may be, it is neither a true inflammation nor a true tumor." Considering the clinical and pathologic findings, it might be said that these cases were instances of acute nonsuppurating thyroiditis which became chronic. If this is true, and I have operated in a sufficient number of cases of Riedel's struma to know the condition when I see it, then it is possible for acute nonsuppurative thyroiditis to metamorphose quickly into chronic nonsuppurative thyroiditis or Riedel's disease.

Considered grossly, these cases cannot be mistaken even if seen early, but it is possible that perithyroiditis has been mistaken for acute nonsuppurative thyroiditis.

We were rather fortunate in obtaining sections from the first case, which we consider to be a very early stage of the disease. In this instance, the surrounding glandular tissue was involved, while recognizable thyroid tissue still remained in the interior of the gland. Thus, it appears that the spread of the fibrous tissue and other pathologic changes occurs from without inward rather than from within outward.

These findings definitely tend to confirm my view that a perithyroiditis is primarily responsible for the woody consistency of the gland and that this fibrous formation does not result from the diseased gland itself. In connection with this last point, I should like to state that I have never seen a true case of Riedel's struma associated with a preexisting goiter, although such cases have been reported.

Perithyroiditis appears to have been a neglected topic in the medical literature. Not even in standard textbooks have I been able to find any mention of perithyroiditis and yet it is not uncommon to find evidence of it when operating for goiter. Most surgeons know that it frequently becomes necessary to use sharp dissection in freeing nodular goiters from their beds. I cannot account for this except by assuming that a perithyroiditis previously existed. In fact, I feel that I am now encountering more of these cases than in years past.

It is possible that the sudden attempted involution which takes place following the administration of iodine in nodular goiter might account for this apparent fixation, but this will have to be proved. Indeed, Boyden, Coller, and Bugher[12] have suggested that iodine administration may be the causative agent in Riedel's struma. However, Zelle and his associates,[8] who cite this theory, remark: "It also seems to us that Riedel's struma was observed before Lugol's solution was used for goiter therapy." These workers also note that this hypothesis does not seem to be convincing in the case which they reported, since the patient had not received this drug for any length of time or in any great quantity.

This last observation likewise holds true in the two cases which I have reported here. In neither instance was treatment with Lugol's solution either prolonged or in large dosage.

We do know, however, that the spectacular involution which follows the use of iodine in diffuse hyperplastic goiters is not forthcoming in the nodular toxic variety. This might possibly be due to the inability of the iodine to reach the glandular tissue because of the dense capsular thickening in these cases, and it is possible that a chemical perithyroiditis (lymphangitis) is effected in the surrounding tissues.

SUMMARY

Let me summarize my views on the etiology of Riedel's struma. It is my opinion that this condition is a vascular rather than a glandular disease, the changes progressing from the outside of the gland rather than from within the organ itself. It begins with a perithyroiditis which induces constriction of the thyroid vessels and associated blood channels. The tissues of the thyroid respond to this ischemia by the formation of the ligneous tissue characteristic of Riedel's thyroiditis.

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FRACTURES OF THE NECK OF THE FEMUR

VERNON L. HART, M.D.* MINNEAPOLIS, MINN.
(From the University of Minnesota Medical School)

IT IS very unusual to observe the two distinct types of fracture of the neck of the femur involving both hip joints of the same individual. I have treated two patients with this interesting situation and wish to report the two cases because the radiograms (Figs. 2 and 3) provide excellent material for instruction.

The two types of fracture of the femoral neck are the abduction or impacted fracture, and the adduction or nonimpacted fracture (Fig. 1). The history, clinical examination, radiographic findings, treatment, prognosis, and complications are so different in each of the two types that their proper recognition is essential.

Since the abduction or impacted fracture of the femoral neck requires no special treatment and always unites, it may be that the study

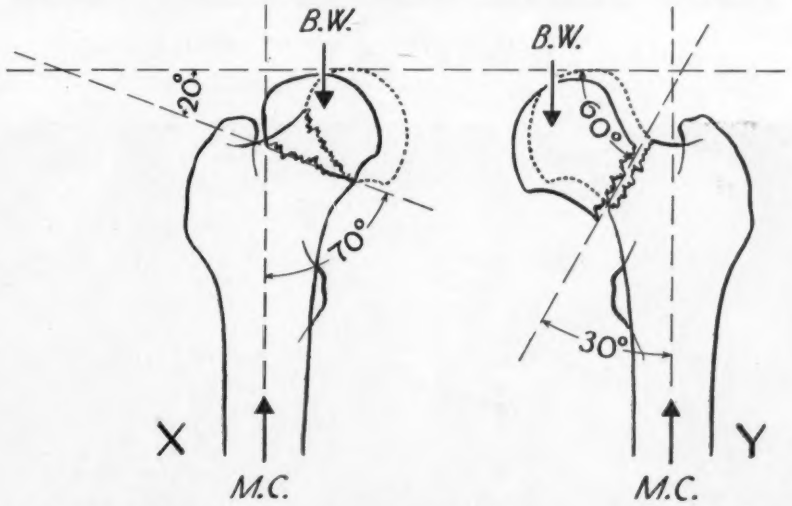

Fig. 1.—*X*, Abduction or impacted fracture; *Y*, adduction or nonimpacted fracture; *B. W.*, body weight; *M. C.*, muscle contraction. The degree of shearing or pressure forces can be expressed by a study of the angle formed between the fracture line and the horizontal line between the two anterosuperior iliac spines (Pauwels) or the angle formed by a line passing through the fracture and a line continuing the axis of the shaft of the femur. (Fracture-shaft angle described by Eyre-Brook and Pridie.) The degree of displacement, pressure, and shearing between the fragments should also be studied in the lateral radiograms.

of this type of fracture, Fig. 2 (*x*) and Fig. 3 (*x*), will provide information for understanding some of the problems which are encountered in the adduction or nonimpacted fracture, Fig. 2 (*y*) and Fig. 3 (*y*). Study of the impacted fracture helps to understand some of the under-

*Major, Medical Corps, U. S. Army, Camp Cooke, Calif.
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Fig. 2. *(For legend see opposite page.)*

Fig. 3. *(For legend see opposite page.)*

lying principles involved in the healing process of fractures of the femoral neck and the importance of mechanical factors on physiologic processes.

The two types of fracture are contrasted in Table I.

The one fundamental principle which is demonstrated by comparing the two types of fracture of the femoral neck is the influence of shearing strain on the healing process of the fracture. In the more common adduction type of fracture, weight-bearing and muscle contraction cause a shearing strain between the fragments with resulting motion, irritation, hyperemic decalcification, absorption of the femoral neck, and nonunion, as shown in Fig. 2 (*y*). To prevent this unfavorable prognosis, the fresh adduction fracture must be accurately reduced and the reduction must be maintained by efficient internal fixation, as in Fig. 3 (*y*), with minimum shearing and maximum pressure forces.

In the rarer abduction type of fracture of the femoral neck, the mechanical forces between the two fragments cause, not shearing, but pressure and impaction. These fractures always unite with bony union without any special form of treatment.

The comparison of these two types of fracture of the femoral neck again emphasizes the principles expressed by Roux and Pauwels that pressure forces between fractured bone fragments stimulate bone production. Shearing strains inhibit bone production and cause irritation,

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Fig. 2.—*X*, (1) Injury six years previously; (2) abduction type of fracture of neck of femur; (3) impaction of fragments by pressure forces; (4) coxa valga deformity; (5) almost horizontal subcapital fracture line (30° angle with the horizontal); (6) there was no displacement or shearing of fragments in the lateral radiogram; (7) pressure forces between the fragments dominated over shearing forces; (8) no special treatment except crutches for several weeks after the injury; (9) solid bony union resulted; (10) no aseptic necrosis after six years; and (11) perfect function of the extremity six years after the injury.

Y, (1) Injury ten months previously; (2) adduction type; (3) no impaction of fragments because shearing forces dominated; (4) coxa vara deformity; (5) fracture line is more vertical and forms an angle of more than 50° with the horizontal; (6) there was displacement and shearing of fragments in both anteroposterior and lateral radiograms (original x-ray studies); (7) shearing forces between the fragments dominated over pressure forces; (8) the fresh fracture reduced by the patient's physician by manipulation under anesthesia, reduction maintained for a period of ten weeks by a Whitman plaster spica; (9) decalcification and absorption of femoral neck resulted from shearing, no bony union; (10) painful weight-bearing, walks with crutches; (11) osteotomy advised to transform shearing forces into pressure forces and to restore gluteal mechanism; and (12) present age, 50 years.

Fig. 3.—*X*, (1) Injury ten years previously; (2) abduction type of fracture of femoral neck; (3) impaction of fragments because of pressure forces; (4) coxa valga deformity; (5) almost horizontal subcapital fracture line which formed an angle of about 30° with the horizontal; (6) no displacement or shearing of fragments in the lateral radiogram; (7) pressure forces between the fragments dominated over the shearing forces; (8) no special treatment except crutches used for several weeks after the injury; (9) solid bony union resulted; (10) no aseptic necrosis of the femoral head after ten years; and (11) perfect function of extremity ten years after injury.

Y, (1) Injury two and one-half years previously; (2) adduction type of fracture of femoral neck (original x-ray studies); (3) no impaction because of shearing (original); (4) coxa vara deformity (original); (5) transcervical fracture line which formed an angle of about 60° with the horizontal (original); (6) displacement and shearing of fragments in both anteroposterior and lateral radiograms (original); (7) shearing forces between the fragments dominated over the pressure forces (original); (8) the fresh fracture was treated by reduction of the fragments and internal fixation with a Smith-Petersen nail, the fragments were immobilized with a mild coxa valga deformity in order to eliminate shearing forces and to contribute pressure forces between the fragments, pressure forces stimulate bone production, and shearing forces inhibit bone production; (9) solid bony union of the fracture, no absorption of the femoral neck and no aseptic necrosis of the femoral head two and one-half years after injury, as demonstrated in the above radiogram; (10) perfect function two one-half years after reduction and nailing of fracture; and (11) present age, 81 years.

TABLE I

FRACTURES OF THE NECK OF THE FEMUR

TYPE	ABDUCTION OR IMPACTED; *x* IN RADIOGRAMS	ADDUCTION OR NONIMPACTED; *y* IN RADIOGRAMS
Incidence	15-20 per cent of all fractures of neck of femur	80-85 per cent
Pain and muscle spasm	Slight	Severe
Disability	May walk after injury without assistance	Marked disability
Deformity of the extremity	No fixed deformity	Adduction and external rotation deformity
Shortening	No	Yes
X-rays	1. Always a subcapital fracture line 2. Always a coxa valga deformity, never a coxa vara deformity 3. Almost horizontal fracture line which forms an angle of not more than 30° with the horizontal line through the anterosuperior iliac spines 4. Impacted fragments because of pressure forces 5. No displacement or shearing of fragments in lateral radiogram 6. Pressure forces between the fragments dominate in both anteroposterior and lateral views 7. Abduction of the distal fragment in relation to the proximal head fragment	1. Subcapital, transcervical, or basal fracture line 2. Coxa vara deformity 3. Fracture line forms an angle of 30 to 90° with the horizontal 4. There is no true impaction. The fragments may overlap slightly and seem to be impacted but are merely entangled. There is a false or pseudo-impaction but never a true impaction 5. Frequent displacement and shearing force in the lateral radiogram 6. Shearing forces dominate over pressure forces in both anteroposterior and lateral views 7. Adduction of the distal fragment in relation to the proximal head fragment
Treatment	Crutches; no special treatment, no plaster splint, no internal fixation. Encourage motion and weight-bearing	Accurate reduction and efficient internal fixation to maintain the reduction with minimum shearing and maximum pressure forces
Bony union	Always unite	High percentage if properly reduced and immobilized by internal fixation
Absorption of femoral neck and nonunion	No	Frequent if not accurately reduced and properly immobilized by internal fixation.
Aseptic necrosis	Infrequent	Relatively frequent
End result	Perfect function if not complicated by aseptic necrosis of femoral head	Depends on accuracy of reduction, efficiency of internal fixation, and complications resulting from circulatory damage and shearing strain

hyperemic decalcification, absorption of the neck of the femur and nonunion. Aseptic necrosis of the femoral head resulting from failure of revascularization is intimately related to the degree of shearing.

The degree of shearing or pressure can be expressed by a study of the angle formed between the fracture line and the horizontal line between the two anterosuperior iliac spines or the angle formed between the fracture line and the shaft-axis line (Fig. 1). This study of mechanical forces should be routine in the examination of all fractures of the neck of the femur because they play a most important role in treatment and prognosis.

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EQUALIZING THE LOWER EXTREMITIES: A CLINICAL CONSIDERATION OF LEG LENGTHENING VERSUS LEG SHORTENING

GEORGE S. PHALEN,* M.D., ROCHESTER, MINN., AND
C. C. CHATTERTON,† M.D., ST. PAUL, MINN.

LOWER extremities unequal in length often produce deleterious effects on the patient from both a mechanical standpoint and a psychologic standpoint.

Mechanically, no more than 4 cm. of shortening of one leg may be compensated for by a tilting of the pelvis; when the shortening is more than this amount, a lift usually must be inserted into the shoe of the short leg to prevent the development of an excessive curvature of the spinal column. Scoliosis and poor posture, with resultant symptoms of strain and fatigue, commonly result from an uncorrected inequality in length of the legs.

Psychologically, a shortened lower extremity because of its attendant disadvantages may be harmful. An elevated shoe, especially if the sole is raised more than 2.5 cm., is conspicuous whether the wearer is walking or sitting, and the wearer of such a shoe may become unhappily self-conscious because of his physical handicap. The weight of the elevated shoe may also be objectional for a patient who has partial paralysis of the muscles in the shortened limb. In addition, the expense of specially built shoes during a lifetime is frequently an important consideration because it is a burden.

Anterior poliomyelitis is one of the etiologic agents which most frequently produce a shortening of a lower extremity. Other causes of shortening include malunited fractures, epiphyseal arrest caused by either injury or infection, congenital dislocation of the hip, arthritis of the hip or knee (especially tuberculous), congenital anomalies, tumors, and chronic infections of bone. It is with these conditions that the orthopedist has chiefly to deal in cases of inequality in length of the lower extremities. Of the forty-five cases reviewed in this paper, the shortening of the leg was due to anterior poliomyelitis in thirty-four cases, to epiphyseal arrest in three cases, to congenital dislocation of the hip in three cases, to arthritis of the hip in three cases, to malunited fracture of the femur in one case, and to congenital shortening in one case.

Occasionally, a leg may be caused to grow longer than its fellow by the presence of a chronic infection of bone, a tumor, or some congenital

*Fellow in Orthopedic Surgery, Mayo Foundation.
†Chief of Staff, Gillette State Hospital for Crippled Children.
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anomaly. The slight increase in length which frequently follows the healing of a fracture seldom necessitates operative intervention.

Length of legs may be equalized by shortening the long leg, by lengthening the short leg, by stimulating growth in the short leg, or by retarding growth in the long leg. Epiphyseodiaphyseal fusion, as described by Phemister, is of definite value in the treatment of inequality in length of the legs during the growing period. The operation usually is performed on the epiphysis at the lower end of the femur or on the epiphyses at the upper end of the tibia and fibula, or on both; arrest of longitudinal growth of the bones, thus, is obtained.

Still in the experimental stage are the operations for activating the epiphyses and for stimulating longitudinal growth of bones either by interruption of medullary blood supply[18] or by peripheral vasodilatation following excision of the lumbar sympathetic rami and ganglia.[23, 29] To date, the results obtained by these procedures are neither spectacular nor convincing. In experimental studies of four normal goats and of one monkey which had residual paralysis from anterior poliomyelitis, Bisgard observed that longitudinal growth of bone was not influenced by sympathetic de-innervation.

We shall limit our discussion in this paper to consideration of the first two methods of leg equalization, that is, leg shortening and leg lengthening.

LEG SHORTENING

The earliest report of a case of operative bone shortening was made by Sayre in 1863; he performed a simple oblique osteotomy of a femur and allowed the fragments to override. Glaessner, in 1907, reported three similar cases. Deutschländer, Calvé and Galland, Taylor, and Groves, suggested procedures for compensatory shortening of the unaffected femur. More recently, White (1935) recommended transverse osteotomy of the femur with overlapping of the fragments and insertion of removable pins to maintain the fragments in correct position. This is a simple and quite satisfactory operative procedure for shortening of the femur. The first report of a case of shortening of the tibia and fibula was made by Brooke,[11] in 1927, and his method is still one of the best employed today.

In a survey of the literature, Wilson and Thompson collected reports of 100 cases of bone shortening, contributed by five authors. In this series there were ninety-eight femoral shortenings and two tibial shortenings. The average shortening obtained was 5 cm.; there were seven cases of postoperative infection and two cases of delayed union.

During the period from 1933 to 1940, inclusive, operations for bone shortening were performed in nineteen cases at the Gillette State Hospital for Crippled Children. The essential data in these cases are summarized in Table I. There were twelve operations on the femur

TABLE I

CASES OF LEG SHORTENING

CASE	DIAGNOSIS	TYPE OF OPERATION	SHORTENING OBTAINED (CM.)	COMPLICATIONS	REMAINING INEQUALITY IN LENGTH (CM.)
1	Poliomyelitis	Z osteotomy of femur; vitallium screws	8.5	None	Legs equal
2	Poliomyelitis	Z osteotomy of tibia; bone screws	5.5	Slight anterior bowing	Legs equal
3	Poliomyelitis	Dovetail tibia; bone screws and Parham band	6.5	Slight posterior bowing; removal Parham band and bone screws	1
4	Congenital dislocation of hip	Z osteotomy of femur; bone screws	8	Separation at osteotomy site; corrected by manipulation	Legs equal
5	Syphilitic epiphysitis	Z osteotomy of femur; Anderson screw	4	None	Legs equal
6	Poliomyelitis	Z osteotomy of femur; Anderson screw	5	Moderate degree relaxation of knee; osteotomy femur to correct lateral bowing 10 months after operation	Legs equal
7	Congenital dislocation of hip	Osteotomy of femur; intramedullary graft	5	None	Legs equal
8	Poliomyelitis	Osteotomy of tibia; intramedullary graft	4.5	Fracture of intramedullary graft 11 months after operation	Legs equal
9	Septic arthritis of hip	Oblique osteotomy of femur; steel nail	5	None	Legs equal
10	Congenital dislocation of hip	Osteotomy of femur; Anderson screw	4.5	Superficial infection; slight anterior bowing	3
11	Tuberculosis of hip	Dovetail femur; nail and wire	4	Slight anterior bowing	5
12	Poliomyelitis	Osteotomy of tibia; intramedullary graft	4	None	Legs equal
13	Poliomyelitis	Z osteotomy of femur; chromic catgut	7.5	Fracture through callus; slight anterior bowing	Legs equal
14	Poliomyelitis	Z osteotomy of tibia; ivory screws	5	Delayed union, 12 months	Legs equal
15	Poliomyelitis	Z osteotomy of femur; Parham bands	3	Osteomyelitis; removal of bands and sequestrum; healed 27 months after operation	3
16	Poliomyelitis	Z osteotomy of femur; wire and two bone screws	4	None	Legs equal

TABLE I—CONT'D

CASE	DIAGNOSIS	TYPE OF OPERATION	SHORTENING OBTAINED (CM.)	COMPLICATIONS	REMAINING INEQUALITY IN LENGTH (CM.)
17	Poliomyelitis	Z osteotomy of tibia; intramedullary graft; vitallium screws	5	Soft tissue infection; delayed union, 8 months	Legs equal
18	Poliomyelitis	Z osteotomy of tibia; vitallium screws	4	None	0.5
19	Osteomyelitis; epiphyseal arrest of femur	Transverse osteotomy of femur; vitallium plate; onlay graft	5	Osteomyelitis; removal of onlay grafts 1 month after operation; wound draining 5 months after operation (at time of report)	Final report not obtained

and seven on the tibia and fibula. Shortening obtained by operation ranged from 4 to 8.5 cm., the average for all the cases being a little more than 5 cm.

The average number of days in the hospital for each of the first eighteen patients in this series was 168; the greatest number, 292; and the least, 101. The majority of the patients began walking with guarded weight bearing, three months after operation. Thomas ring caliper braces were worn for another three to six months in most of the cases of femoral shortening; and walking casts were worn for another six to twelve weeks in most of the cases of tibial shortening.

There are definite disadvantages to the operation of bone shortening. It is most important for the surgeon to realize that this operation is performed on a normal extremity in the presence of an extremity that is already abnormal. This jeopardizing of the well leg makes any postoperative complication all the more serious and costly. A patient who has only one normally functioning leg will think twice before consenting to any elective operative procedure on the well member. A lift on the shoe of the short leg, no matter how unsightly, would certainly be preferable to a postoperative disability of the previously normal longer leg.

If a patient is approximately 6 feet (183 cm.) tall, a bone-shortening operation would ordinarily be recommended rather than a bone-lengthening procedure. However, when the height of the patient is only 5½ feet (168 cm.), or less, the surgeon is not so hasty to suggest a further 2 or 3 inches (5 or 7.5 cm.) shortening of stature. Women, of course, can better afford to lose a few inches in height than can men; short stature is never so much of a physical handicap to a woman as it is to a man. Furthermore, a loss in height may become a mental handicap.

The shortening may be "humiliating" in the true etymologic sense of the word, "to make nearer the ground."[37] A man who is less than 5 feet 5 inches (165 cm.) tall probably would prefer to wear a lift on his shoe for the rest of his life than to lose 2 or 3 inches (5 or 7.5 cm.) in height.

We believe that a leg-shortening operation should not be performed until after the growth of the patient has been well attained. The postponement obviates the necessity of using any formula, such as that recommended by Brooke,[12] to determine the additional amount of shortening which will be required after the patient's growth has ceased. In the series of nineteen cases reported herein, the average age of the patients was eighteen and one-half years; the youngest patient was sixteen and the oldest, twenty-one years of age. If, at the time of operation, the cause of the shortening is still active, continuation of the disturbed rate of growth will lead later to discrepancy in the length of the limbs. Some authors suggest that the hyperemia resulting from the shortening operation also may lead to an increased rate of growth of the shortened leg.

LEG LENGTHENING

Surgical procedure for bone lengthening is much newer than that for bone shortening. Codivilla, in 1905, was the first to devise a method for lengthening long bones; he performed osteotomy and then applied direct skeletal traction by means of a nail through the os calcis. In a series of twenty-two cases, Codivilla obtained gains in length of 3 to 8 cm. In 1908, Magnuson demonstrated experimentally that leg lengthening could be performed without damage to the blood supply or nerve function of the extremity. Using an apparatus called an "osteoton," which provided continuous skeletal traction, Putti,[31] in 1921, succeeded in obtaining 7.5 to 10 cm. lengthening in ten cases of femoral shortening; in all these cases union was somewhat delayed. It remained for Abbott[1-4] to devise a simple dependable apparatus, to standardize the operative procedure, and to place the operation of leg lengthening on a practical basis. Since Abbott's first report, in 1927, of six cases in which bones were lengthened successfully, the operation has been performed on hundreds of patients by various orthopedic surgeons throughout the country. There have been, of course, minor variations in the technique of operation and in the lengthening apparatus employed.[6, 7, 9, 21, 22, 24, 26, 38] Most surgeons prefer to lengthen the tibia and fibula, but Anderson expressed the belief that it is wiser to lengthen the femur.

Wilson and Thompson collected reports of 270 cases of bone lengthening which had been contributed by eleven different authors; of these cases the surgical procedure in 224 was lengthening of the tibia and fibula and in forty-six, of the femur. The maximal amount of lengthening obtained from either the tibia or the femur was 9 cm. and the maximal lengthening from both bones, 11.5 cm. Postoperative complica-

tions included infection in twenty-two cases, delayed union in five cases, nonunion in twelve cases, fracture in ten cases, and injuries to nerves in five; there was one death.

During the period from 1928 to 1940, inclusive, operations for leg lengthening were performed in twenty-six cases at the Gillette State Hospital. Table II presents a summary of data in these cases. There were two cases of femoral lengthening, twenty-three cases of tibial lengthening, and one case in which both femur and tibia were lengthened. The amount of lengthening obtained by operation ranged from 0.5 to 7.5 cm., the average for all cases being 4.5 cm.

The average number of days in the hospital for each of the patients in this series was 244.5, the greatest number was 552, and the least number, 87. The patient who stayed in the hospital 552 days had a lengthening of both tibia and femur. The majority of the patients began walking, with guarded weight bearing, about four months after operation. Thomas ring caliper braces or short Hessing braces were worn for another three to six months in most of the cases.

From the data recorded in Table II it is evident that no one of the three femoral-lengthening operations was satisfactory. In each of the three cases an attempt was made to obtain lengthening without skeletal countertraction. We agree with Putti[32] and Abbott[2] that skeletal countertraction is an essential principle of a leg-lengthening procedure.

In most of the cases, of which Figs. 1, 2, and 3 are typically illustrative, a tongue and groove osteotomy of the tibia was performed. The steps of this operation are as follows: tenotomy of the Achilles tendon, transverse osteotomy of the fibula, insertion of one Steinmann pin in the lower end and two pins in the upper end of the tibia, tongue and groove osteotomy of the tibia between the pins, cutting of all tight fascial and periosteal bands, and application of the leg-lengthening apparatus. The osteotomy of the tibia is performed through a long, curved, anteromedian incision; the tibial shaft is exposed, and, with the double blade motor saw, a long double cut is made through the anterior osseous cortex. These two vertical saw cuts are joined below by a transverse cut anteriorly and above by means of Gigli's wire saw posteriorly. This leaves the tongue graft above and the groove below.

The apparatus employed in all of the tibial lengthenings was a modification devised by Cole, in 1927, of Abbott's original apparatus. This modified apparatus enables the surgeon to carry out the three principles so necessary for a successful operation for leg lengthening, that is, employment of skeletal traction and countertraction, application of slow continuous traction, and maintenance of accurate contact and alignment of the fragments.

Before an operation for leg lengthening is performed, the patient should try wearing an elevated shoe, not only to correct secondary conditions such as scoliosis and poor posture, but also to determine the amount of lengthening which will give the optimal improvement in

TABLE II

CASES OF LEG LENGTHENING

CASE	DIAGNOSIS	TYPE OF OPERATION	LENGTH OBTAINED (CM.)	COMPLICATIONS	REMAINING INEQUALITY IN LENGTH (CM.)
20	Poliomyelitis	Tongue-groove osteotomy of tibia	3	Lower pin broken before lengthening complete	4
21	Poliomyelitis	Tongue-groove osteotomy of tibia	2.5	Upper pins broken before lengthening complete	4
22	Epiphyseal arrest, septic arthritis of knee	Z osteotomy of femur; tongs in condyles	3	Method of traction not satisfactory	10
23	Poliomyelitis	Tongue-groove osteotomy of tibia	0.5	Lower pin broken; fracture tongue graft; drainage; sequestrectomy 12 months after operation	6.5
24	Poliomyelitis	Tongue-groove osteotomy of tibia	3	Drainage around pins; curettement of sinuses 7 months after operation	6
25	Poliomyelitis	Tongue-groove osteotomy of tibia	2.5	Area around incision slow to heal; persistent ulcer here was grafted 31 months after operation	2.5
26	Poliomyelitis	Tongue-groove osteotomy of tibia	4.5	None	1
27	Poliomyelitis	Tongue-groove osteotomy of tibia	4.5	None	Legs equal
28	Poliomyelitis	Tongue-groove osteotomy of tibia	6.5	Plastic closure sinus 7½ months after operation; curettage of sinus 9 months after operation	Legs equal
29	Poliomyelitis	Tongue-groove osteotomy of tibia	5	Drilling for nonunion 12 months after operation	5
30	Poliomyelitis	Tongue-groove osteotomy of tibia	4	Draining sinuses 6 months after operation	Legs equal
31*	Poliomyelitis	Tongue-groove osteotomy of tibia	5.5	None	5
		Vertical osteotomy of femur	1.5	Upper pin broken; apparatus removed and 20-pound traction to lower pin; drainage about pins; tibial graft for nonunion femur 9 months after operation; fractured shaft femur 39 months after operation	4
32	Poliomyelitis	Tongue-groove osteotomy of tibia	6.5	Fracture tongue graft 5 months after operation	1

TABLE II—CONT'D

CASE	DIAGNOSIS	TYPE OF OPERATION	LENGTH OBTAINED (CM.)	COMPLICATIONS	REMAINING INEQUALITY IN LENGTH (CM.)
33	Poliomyelitis	Tongue-groove osteotomy of tibia	7	Pedicle graft to ulcer of lower leg 5 years after operation; pinch graft to another ulcer 7 years after operation	Legs equal
34	Poliomyelitis	Tongue-groove osteotomy of tibia	6	None	Legs equal
35	Poliomyelitis	Z osteotomy of tibia	2.5	None	2.5
36	Poliomyelitis	Tongue-groove osteotomy of tibia	4	Delayed union, 11 months after operation; supracondylar osteotomy of femur for genu valgum 6 years after operation	5
37	Poliomyelitis	Tongue-groove osteotomy of femur; Roger Anderson apparatus	1	Apparatus removed; 13-pound traction applied; fracture tongue graft	5
38	Congenital shortening	Tongue-groove osteotomy of tibia	4	Drainage upper end of wound; chicken pox	4
39	Poliomyelitis	Tongue-groove osteotomy of tibia	6.5	Removal of protruding portion of tongue graft 5 months after operation; osteomyelitis healed 14 months after operation	1
40	Poliomyelitis	Tongue-groove osteotomy of tibia	7	Lower pin broken and replaced	Legs equal
41	Poliomyelitis	Tongue-groove osteotomy of tibia	4.5	Slight drainage, lower pin	0.5
42	Poliomyelitis	Tongue-groove osteotomy of tibia	4	Lower pin broken and replaced	Legs equal
43	Poliomyelitis	Tongue-groove osteotomy of tibia	7.5	None	4.5
44	Septic arthritis of hip with dislocation	Tongue-groove osteotomy of tibia	5	Temporary peroneal hypesthesia	5
45	Old fracture of shaft of femur	Tongue-groove osteotomy of tibia	5	Tongue graft exposed in incision; fastened with two vitallium screws 7 months after operation; not healed 11 months after operation	1.5

*In Case 31 two operations were performed.

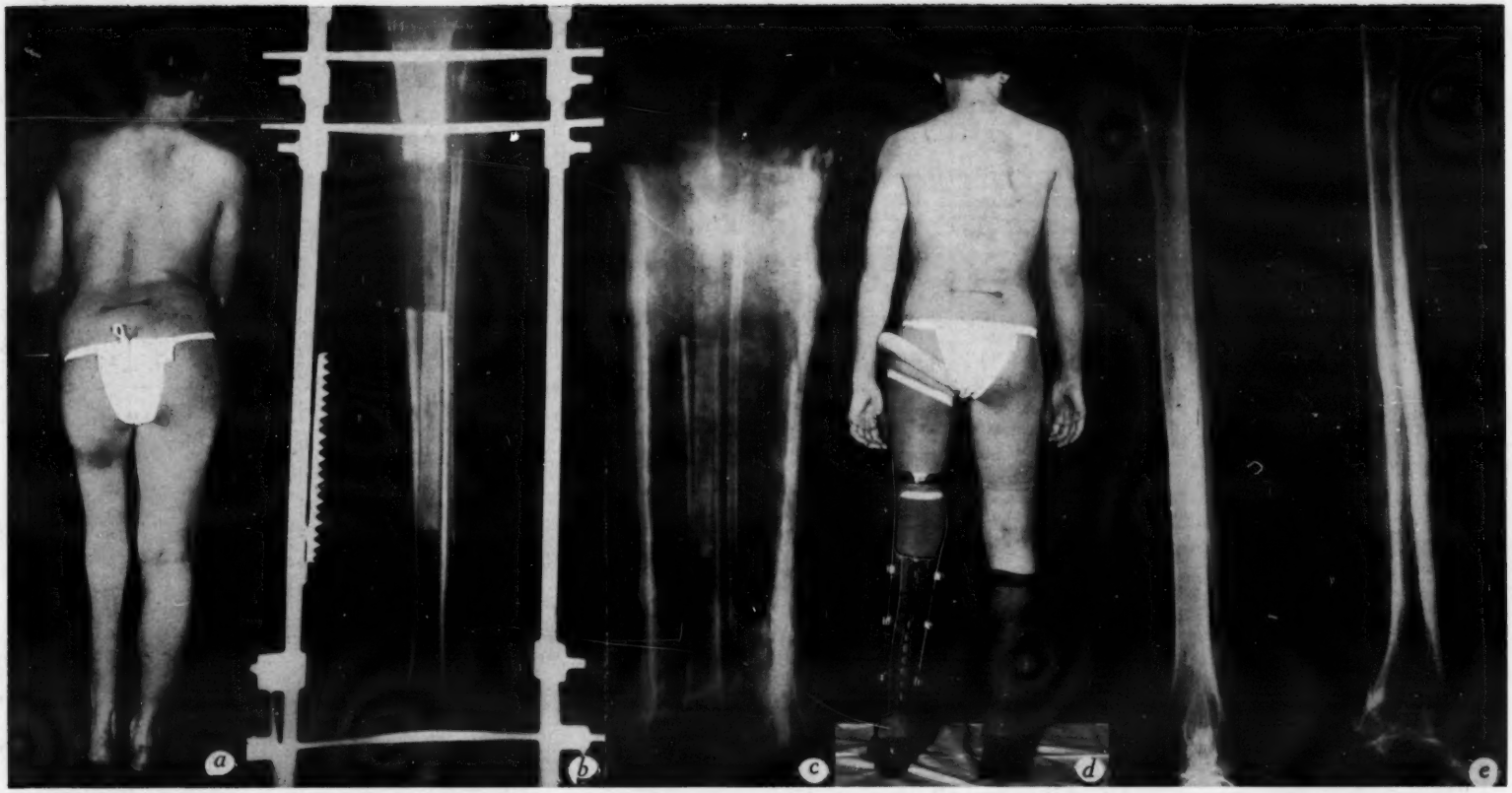

Fig. 1.—Lengthening of the tibia and fibula, Case 33; *a*, posterior view of the patient on admission, left leg 7 cm. shorter than right; *b*, left tibia and fibula in the leg-lengthening apparatus, five weeks after operation; *c*, left tibia and fibula in plaster cast after removal of pins and apparatus, three months after operation; *d*, posterior view of patient on discharge, eight months after operation; patient is wearing a Thomas ring caliper brace and legs are equal in length; *e*, anteroposterior and lateral views of left tibia and fibula four years after operation.

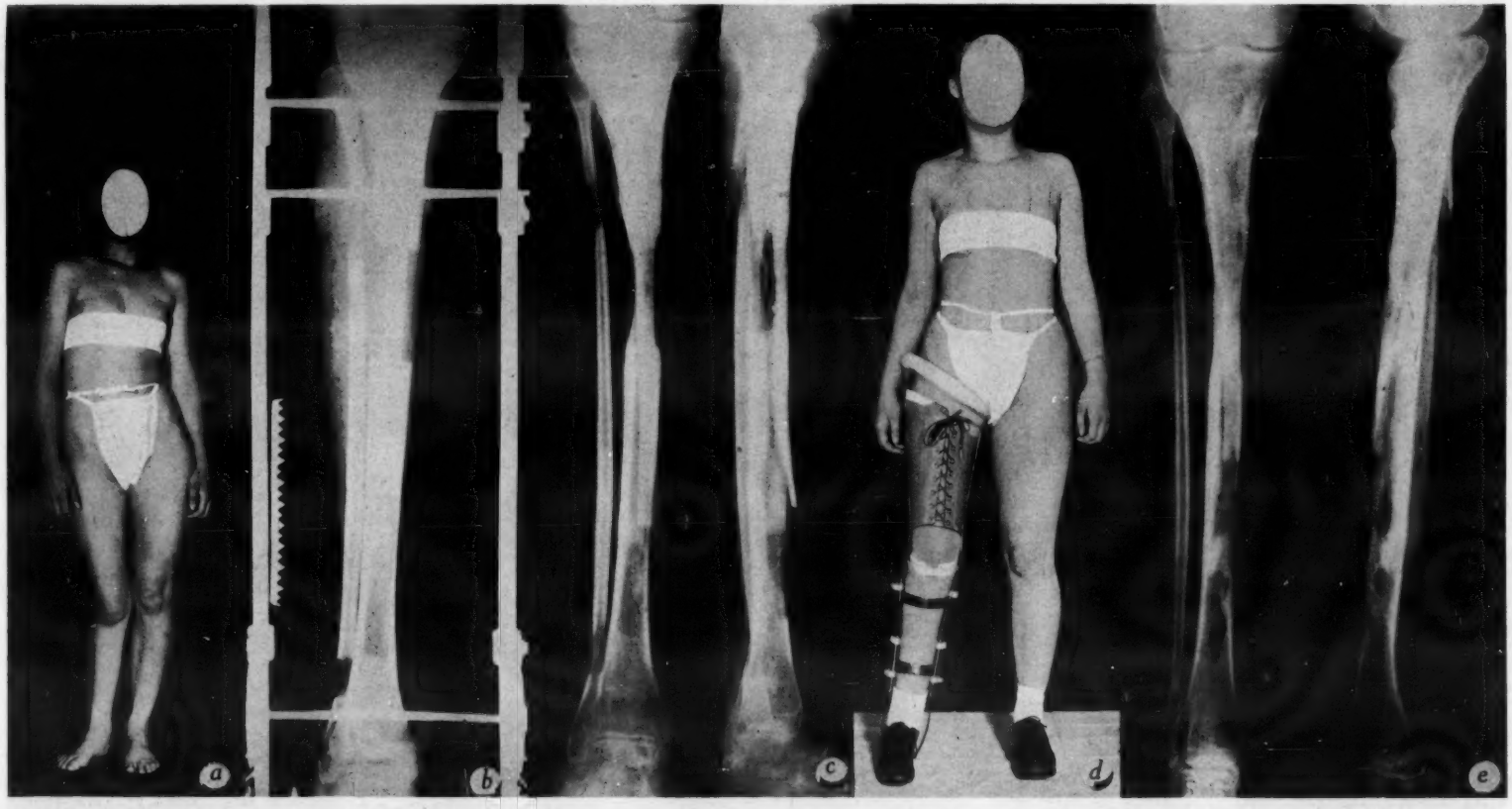

Fig. 2.—Lengthening of the tibia and fibula, Case 28; *a*, anterior view of the patient on admission, right leg 6.5 cm. shorter than left; *b*, right tibia and fibula in the leg-lengthening apparatus, five weeks after operation; *c*, anteroposterior and lateral views of right tibia and fibula, seven months after operation; plastic closure of sinus, through which distal end of tongue graft projected, was done at this time; *d*, anterior view of the patient on discharge, one year after operation; patient is wearing a Thomas ring caliper brace and legs are equal in length; *e*, anteroposterior and lateral views of right tibia and fibula, twenty months after operation.

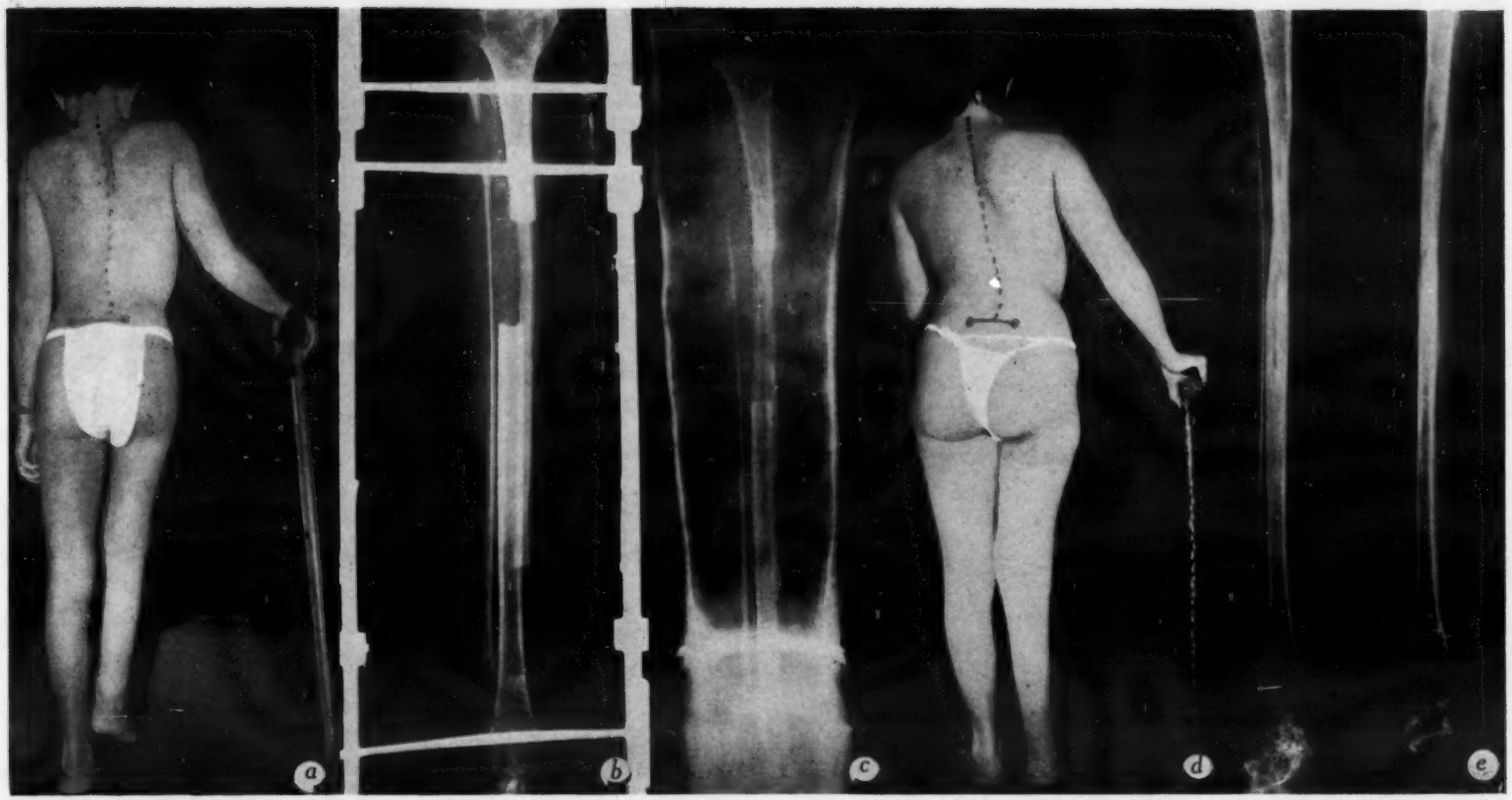

Fig. 3.—Lengthening of the tibia and fibula, Case 43; *a*, posterior view of the patient, right leg 12 cm. shorter than left; *b*, right tibia and fibula in the leg-lengthening apparatus, one month after operation; *c*, right tibia and fibula in plaster cast after removal of pins and apparatus, five months after operation; *d*, posterior view of the patient seventeen months after operation; right leg is still 4.5 cm. shorter than left and patient must wear a long leg caliper brace; *e*, anteroposterior and lateral views of right tibia and fibula, twenty-one months after operation; both bones are very thin.

function. Whether or not there is a fixed pelvic obliquity should also be determined before operation. If the abductor muscles of the hip are weak, as they frequently are in cases of poliomyelitis, equalization of the lower legs and consequent leveling of the pelvis will so change the leverage of these weakened muscles that the gait may be worse after the lengthening than before the operation. At least one case has been reported in which the hip gradually dislocated after a lengthening operation upon the tibia.[27] A child who has very weak hip muscles walks better if the paralyzed leg is at least one-half inch shorter than the normal leg. We believe it is not advisable to perform a leg-lengthening operation of any type unless the quadriceps and abductor muscles of the hip are strong.

An operation for leg lengthening is not indicated unless there is a shortening of more than 2.5 cm. that is producing impairment of gait. Clinical or roentgenographic evidence of previous infection or other pathologic involvement of the bones of the short extremity contraindicates the operation for bone lengthening. Another contraindication is a shortening of so marked a degree that the maximal lengthening even of both the tibia and femur will not sufficiently equalize the extremities. In these rare cases, amputation and the use of artificial limbs will give better functional results.

We believe it is preferable for the patient to be at least 14 to 16 years of age before undergoing the operation, although in this series of twenty-six cases, eight patients were less than 14 years old. The youngest patient was 9 and the oldest 21 years old; the average age for the twenty-six patients was 15½ years of age.

Leg lengthening is a somewhat formidable and technically difficult operative procedure entailing a prolonged period of disability and a risk of numerous complications of which the more important are postoperative infection, delayed union or nonunion, paralysis of nerves caused by stretching, circulatory disturbances (prolonged edema, chronic ulcers, thrombosis, and so forth), breaking of the metal traction pins, and fracture of the tongue graft. Other complications reported in the medical literature[10, 16, 33, 34] include late fractures, malunion, necrosis of skin and bone, traumatic arthritis and lessened motion in the knee, deformity of the foot, protrusion of the tongue graft through the skin, displacement of the head or the distal end of the fibula when this bone unites prematurely and is not lengthened as much as the tibia, and increased weakness of the lengthened muscles in cases of poliomyelitis. Not all these types of complications occurred in the series of cases reported in this paper; those which were encountered are listed in Table II.

LEG LENGTHENING VERSUS LEG SHORTENING

The operation for lengthening of a shortened extremity always has held an irresistible appeal for surgeons and patients alike. We believe,

however, that for the majority of patients who have shortening of one of the lower extremities, an operation for leg shortening is preferable to an operation for leg lengthening.

The operation for leg lengthening does have certain decided advantages over the procedure for leg shortening. The latter is performed on the abnormal extremity and the well leg is not jeopardized. Furthermore, height is not sacrificed by an operation for leg lengthening; as we have stated previously, a loss in height may be a marked physical or mental handicap to a patient of less than average stature.

The operation for leg shortening, however, is relatively simple and safe, and the procedure is accurate. The shorter period of disability after an operation for leg shortening as compared with the period of disability after an operation for lengthening means a great saving of time and money for the patient. The short leg nearly always is found to be ill adapted to plastic operations; especially as a result of poliomyelitis, the short leg has weak, atrophic muscles, slender bones (Fig. 3), and a relatively poor blood supply. The sound limb is much better suited than the weakened limb to withstand a major surgical procedure. In most cases of inequality of the lower extremities, the operation for leg shortening offers a mechanical advantage in that lowering of the center of gravity of the body tends to increase bodily stability and improve locomotion.

SUMMARY

There have been presented forty-five cases in which operations for equalization of the lower extremities were performed. Twenty-six of the patients had operations for leg lengthening and nineteen had operations for leg shortening. Although serious complications may be encountered subsequent to either type of operation, the advantages of the procedure for leg shortening greatly outweigh those of the operation for leg lengthening. The latter, more formidable operative procedure had probably best be limited to that small, carefully chosen group of patients who have unequal lower extremities and who are either unwilling or ill able to sacrifice any fraction of their height.

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THE SURGICAL TREATMENT OF PILONIDAL CYSTS

With a Description of the Author's Method of Demarcation and Closure

Guy S. Van Alstyne, M.D., Chicago, Ill.

SURGICAL removal of a pilonidal cyst can be facilitated by accurate mapping of the cystic area on the overlying skin. Successful primary closure of the wound is possible only if dead spaces in which blood or serum may accumulate can be prevented.

An almost universal method of mapping out the cyst cavity has been the injection of a methylene blue solution through the sinus that is always present. Gage[1] and others have emphasized that if a dye is injected into these sinuses for the purpose of delineating all of the ramifications of the cyst cavity, it must be injected several days prior to operation. By so doing, the lining will become deeply stained, but the dye will not run and stain newly cut tissue, as happens when its injection is done at the time of operation. The dye method, even with this suggested improvement, however, does not map out the area on the overlying skin, but simply tells the surgeon when he has not excised widely enough.

Many methods of primary closure have been advocated. All have been designed to close accurately the dead space between skin and sacrococcygeal fascia. Lahey,[2] in 1929, after block excision of the cyst, filled the gap with a pedicle flap. In 1932,[3] he modified this by shifting a flap attached at both ends, leaving a crescentic space over one gluteal region to granulate. Cattell[4] still further modified this in 1934, closing this gap by converting the crescent into a "Y." Burgess[5] advocates primary closure by undermining the edges of the wound, then placing silk retention sutures tied over a rubber sponge or gauze. This method, he feels, aids in obliterating the dead space in question. Ferguson and Mercray[6] describe a method of primary suture in which a single mattress suture of alloy steel wire is tied over a gauze roll on either side, or a double mattress suture simulating a double figure-of-eight suture is similarly tied.

In my opinion all of these and similar methods fail to obliterate the dead space between skin and deep fascia because they do not take into consideration the natural depression between the nates in which these cysts usually lie. Instead of restoring this groove, they bridge the skin over it, creating a dead space and so inviting infection.

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The method of excision and closure which I have used for many years fulfills these two requirements: it maps out the area accurately on the overlying skin; it restores the natural groove between the nates, and so entirely obliterates all space between the skin and the sacrococcygeal fascia.

Fig. 1.

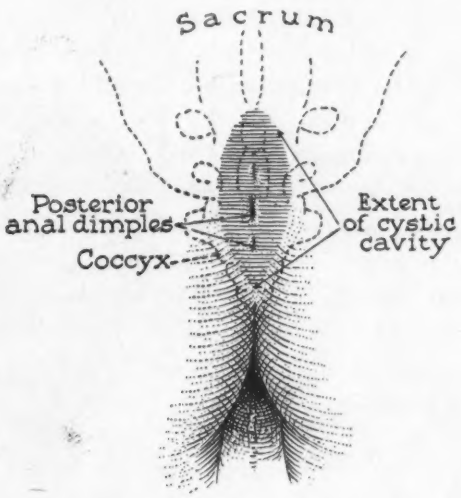

Fig. 2.

Fig. 3.

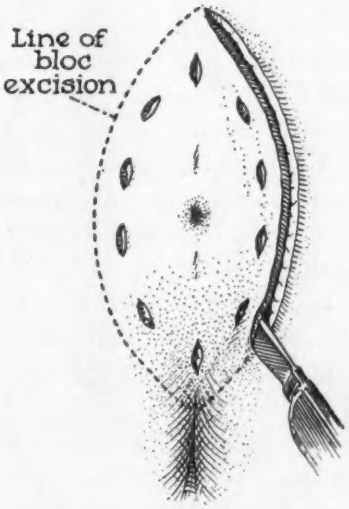

Fig. 4.

TECHNIQUE

First pass a small probe (Fig. 1) through the postanal dimple (Fig. 2) into the cavity of the cyst and push it cephalad as far as possible

using care, however, not to make a false passage into the pericystic tissues. Now make a small nick in the skin over the palpable head of the probe. Next change the position of the probe to an oblique, both right and left, nicking the skin each time over the head as before. Continue this to a transverse position, then obliquely downward and lastly, directly caudad. This series of skin nicks now accurately maps out the cyst area on the skin surface.

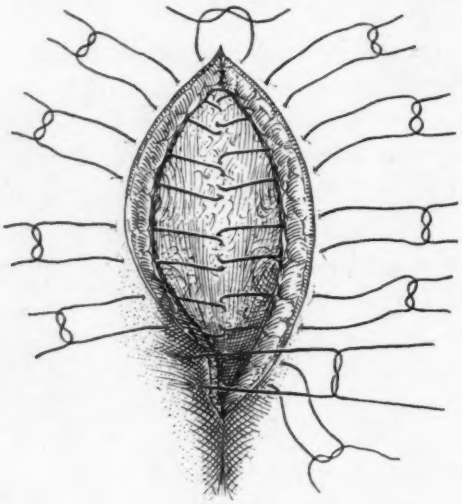

Fig. 5.

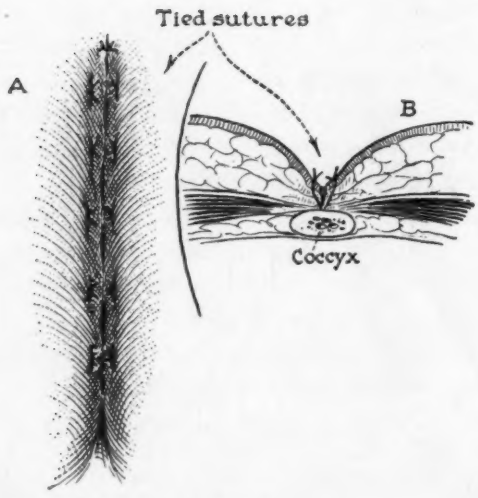

Fig. 6.

Next inject a bismuth paste (Fig. 3). This will distend the cyst, and identify any ramification which an unwary surgeon might inadvertently cut, better, I believe, than methylene blue or other dye can.

With the area accurately delineated on the skin one can now excise the cyst *en bloc* by cutting widely around the marked-out area (Fig. 4).

To close,* instead of suturing the edges of the skin flaps to each other, I place mattress sutures of heavy silk very close to the edge of one side, then through the deep fascia overlying the lower sacrum and coccyx in the midline or very slightly past it, then back again through the edge of the same flap (Fig. 5). Sufficient similar sutures are placed along each flap edge from skin to fascia and back so that when tied, each flap is folded on itself with its free edge now held firmly to the bottom of the groove in the midline (Fig. 6). This procedure approximates the edges just as truly as though they were sutured to each other with the additional advantage of entirely obliterating any possible dead space underneath. One or more shallow sutures may be placed from one flap to the other (Fig. 6 *A*, top suture) should there be any gap, excepting that it is wise, since these cysts are always infected, and since this region is close to the anus, to leave a small gap at the lower angle for drainage.

*The author, in describing this method of closure, had, until April 20, 1942, believed it original with himself. On that date he was informed that practically an identical procedure had been described by Colp[7] in 1929.

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THE ANTIBACTERIAL ACTION OF CERTAIN DISINFECTANTS

ANSON HOYT, M.D., ROY T. FISK, AND GERHARD BURDE
LOS ANGELES, CALIF.

(From the Laboratories of the Los Angeles County Hospital (Unit One) and the Department of Bacteriology, School of Medicine, University of Southern California)

FROM the time of Robert Koch it has been a commonly accepted belief that mercury bichloride is an efficient germicide for the destruction of bacterial spores as well as vegetative forms of microorganisms. More recently certain inorganic and numerous organic mercurial preparations have been popularized and widely employed as chemical disinfecting agents.

In spite of their popularity mercurial disinfectants have certain disadvantages. Bichloride of mercury is markedly toxic, irritating, and corrosive. Some of the newer mercurials and, especially, certain organic compounds show considerable improvement in these respects. The main defect of the mercurials, however, lies in their high bacteriostatic powers in comparison with their bactericidal abilities; they often prevent bacteria from multiplying without actually killing them. As a result of such bacteriostasis the mercurials tend to give falsely high phenol coefficient values and show spectacular results when tested by the agar cup plate technique.

The relatively high bacteriostatic and low bactericidal power of bichloride of mercury was first reported by Geppert (see Welch[1]), in 1889, and was well recognized by Welch[1] and his co-workers as early as 1891. More recently it has become evident that the actual bactericidal or bacteria-killing powers of practically all mercurial disinfectants are remarkably low, a fact which was lately (1940) emphasized by a report of the Council of Pharmacy and Chemistry of the American Medical Association.[2] Brewer[3] (1939) demonstrated that organic mercurial compounds cannot be relied upon for killing spores which may contaminate surgical and dental instruments, sutures and other materials. It is also easy to show with the use of sodium thioglycolate medium (Brewer[4]) that many mercurial disinfectants, in the concentrations customarily employed, are unable to kill certain nonspore-forming bacteria. The experiments here reported are mostly tests performed for the Los Angeles County Hospital on the bactericidal efficacies of certain mercurials in comparison with aqueous iodine plus potassium iodide and also with aqueous zephiran (Alba).

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The following technique was employed for most of the experiments. Eighteen-hour broth cultures of *Staphylococcus aureus* and of *Escherichia coli* were used as test organisms. Various dilutions of the disinfectants were made in 5 c.c. volumes in distilled water. One-half cubic centimeter of a test culture was pipetted into 5 c.c. of each disinfectant, mixed and allowed to stand at room temperature. After five and ten minutes, subcultures were made with an approximately standard phenol coefficient loop into tubes containing about 10 c.c. of (a) plain broth and (b) sodium thioglycolate broth. These subcultures were incubated at 37° C. for a minimum of forty-eight hours and observed for growth. Random subcultures showing growth were stained by Gram's method and examined for contamination but no contamination was observed. Tables I and II are illustrative of the results obtained and represent experiments that were performed at the same time on the germicidal activities of aqueous iodine and mercuric chloride against *E. coli*.

TABLE I

ACTION OF AQUEOUS IODINE PLUS POTASSIUM IODIDE ON *E. coli*

DILUTIONS OF 1% AQUEOUS IODINE PLUS 2% POTASSIUM IODIDE	5-MINUTE SUBCULTURES		10-MINUTE SUBCULTURES	
	PLAIN BROTH	SODIUM THIOGLYCOLATE BROTH	PLAIN BROTH	SODIUM THIOGLYCOLATE BROTH
Full strength	–	–	–	–
1/4	–	–	–	–
1/16	–	–	–	–
1/64	–	–	–	–
1/256	+	+	+	+

+ = Growth
– = No growth
} of *E. coli* in ninety-six hours

TABLE II

ACTION OF MERCURIC CHLORIDE ON *E. coli*

DILUTIONS OF 1/1000 MERCURIC CHLORIDE	5-MINUTE SUBCULTURES		10-MINUTE SUBCULTURES	
	PLAIN BROTH	SODIUM THIOGLYCOLATE BROTH	PLAIN BROTH	SODIUM THIOGLYCOLATE BROTH
Full strength	–	+	–	+
1/4	–	+	–	+
1/16	–	+	–	+
1/64	–	+	–	+
1/256	+	+	+	+

+ = Growth
– = No growth
} of *E. coli* in ninety-six hours

Table I indicates that 1 per cent aqueous iodine in dilutions up through 1/64 apparently killed the test organisms. No growth was observed in the subcultures made into plain broth or sodium thioglycolate broth until dilutions of aqueous iodine exceeding 1/64 were tested. Table II shows a very contrasting picture. Subcultures into plain broth failed to grow until they were made from an original 1/256 dilution of the 1/1000 mercuric chloride, whereas all the sodium thioglycolate broth subcultures showed growth. This test indicates that bichloride of mercury

has a marked bacteriostatic rather than a bactericidal action. It inhibited growth by bacteriostasis in most of the plain broth subcultures but failed to do this in sodium thioglycolate broth. Many sulfur-containing compounds, and especially sodium thioglycolate, can neutralize the bacteriostatic action of mercurials and allow bacteria, which are inhibited but not killed, to multiply once more. It is of interest to consider in this connection that various sulfur-containing compounds are present in the human body. Aqueous iodine 1 per cent, in contrast to mercuric chloride, showed an apparent bactericidal effect in dilutions up through $\frac{1}{64}$ and its bacteriostatic action likewise disappeared above this point.

Table III summarizes all experiments on the disinfectants that were tested by the above methods. As a result of the use of sodium thioglycolate broth as one of the subculturing mediums, the effective germicidal strengths of the mercurials are shown to be surprisingly low although they would have appeared extremely efficacious if subcultures had been made only into plain broth.

TABLE III

SUMMARY OF DISINFECTANTS TESTED

DISINFECTANT	NUMBER OF EXPERIMENTS	HIGHEST FINAL DILUTION OF DISINFECTANT WHICH PROVED EFFICACIOUS IN TEN MINUTES OF ACTION AT ROOM TEMPERATURE AGAINST	
		Staph. aureus	*E. coli*
Mercurials			
Mercurochrome (aqueous)	1	Less than $\frac{1}{20}$	Less than $\frac{1}{20}$
Mercuric chloride	1	Less than $\frac{1}{1000}$	Less than $\frac{1}{1000}$
*Phenylmercuric acetate (cystan)	4	Less than $\frac{1}{1000}$	Less than $\frac{1}{1000}$
Tincture metaphen	1	Less than $\frac{1}{1000}$	Less than $\frac{1}{1000}$
Merthiolate solution	1	Less than $\frac{1}{1000}$	Less than $\frac{1}{1000}$
Tincture mercoseptic	1	$\frac{1}{1000}$	$\frac{1}{4000}$
Nonmercurials			
Aqueous iodine (plus double concentration of KI)	4	$\frac{1}{6400}$	$\frac{1}{6400}$
Zephiran (aqueous)	4	$\frac{1}{16,000}$	$\frac{1}{4000}$

*This is approximately four times the strength of cystan that is recommended by its manufacturer for the sterilization of cystoscopes and other instruments.

Prolonged contact with at least one of the mercurials at room temperature was shown to exert a bacteriostatic but no bactericidal effect. In three experiments, phenylmercuric acetate (cystan) was employed in the concentration recommended for cystoscope sterilization (approximately $\frac{1}{3800}$). *Staph. aureus* was left in contact with this disinfectant for periods ranging up to two and one-half hours. Subcultures into sodium thioglycolate broth showed luxuriant growth after the longest period of exposure, although the subcultures that were made into plain broth, at all intervals from five minutes to two and one-half hours, failed to grow.

Mercuric cyanide, 1/1000, was tested in a different manner inasmuch as subcultures were made into blood broth and blood agar after varying periods of exposing *Staph. aureus* to this chemical. Staphylococcus colonies too numerous to count were observed in blood plates poured after exposures up to and including twenty-four hours and all the blood broth subculture tubes showed growth.

Zephiran and aqueous iodine have a number of advantages which will be noted briefly. Zephiran is but slightly toxic on intraperitoneal injection into mice; several normal mice tolerated 1/1000 aqueous zephiran in doses of 0.01 c.c. per gram of body weight by the intraperitoneal route, although deaths were encountered when this dose was doubled. Aqueous zephiran, 1/1000, appears to be practically nontoxic when taken by mouth. A mouse was given dry food with 1/1000 aqueous zephiran as its only source of fluid for a period of two months; the mouse suffered no ill effects and was still living and well one month after the conclusion of this test. Aqueous zephiran is nonirritating to skin, has a low surface tension, and acts as a fairly efficient detergent. It is also relatively nonirritating to open wounds and to mucous membranes and is being used increasingly as a germicide for skin preparation and also for the irrigation of infected wounds, sinuses, and cavities. Zephiran seems also adapted for the chemical sterilization of instruments which cannot be exposed to heat. It evidently has little corrosive action other than that of the water in which it is dissolved. It was shown to have no deleterious effect upon the type of cement employed in cystoscopes. In one test a portion of a cystoscope was immersed for seventeen days at room temperature in 1/1000 aqueous zephiran without the occurrence of any noticeable corrosion of the metal or injury to the cement. In order to minimize corrosion it has been recommended that 0.5 per cent sodium nitrite be added to aqueous zephiran when this disinfectant is used for the storage of metal instruments.

Both zephiran and aqueous iodine appear to have bactericidal powers, against the test organisms employed, in dilutions approximately as high as those showing bacteriostasis. Iodine, when improperly used, has and can cause severe burns. It is our opinion, however, that iodine could well be utilized for skin preparation in dilutions considerably higher than those commonly employed. This would minimize the chance of iodine burns and should still be effective. It has been shown that aqueous iodine, in concentrations that cause little irritation to tissues, can still act as an effective germicide. Salle and his associates,[5] working with their "toxicity index" technique, compared a number of disinfectants and reported that aqueous iodine exhibited the least toxicity to tissues, relative to its bacteria-killing ability, of all disinfectants tested. Thompson, Isaacs, and Khorazo[6] checked the action of various disinfectants against a strain of *Staph. aureus,* using the germicides in their maximum nonirritating concentrations as determined by instillation on the corneas

of albino rabbits; they reported that zephiran showed the most marked and rapid disinfecting action and iodine also placed relatively high in this respect. Since iodine has the disadvantage of being corrosive to metals, it should not be employed routinely for the cold sterilization of instruments although it might serve as a valuable emergency sterilizing agent.

DISCUSSION

The ideal disinfectant for skin preparation, for the irrigation of infected wounds and cavities, and for the cold sterilization of instruments has not been demonstrated to date. Laboratory tests, such as those here reported, are mainly of value as an argument against the use of mercury-containing compounds which can easily be shown to have high bacteriostatic but low bactericidal powers. Aqueous iodine and zephiran both appear to possess high bactericidal powers as well as high bacteriostatic abilities; it is only fair to add, however, that any compound showing apparently high bactericidal powers may eventually be proved to act mainly by bacteriostasis provided that a proper subculturing medium, analogous to sodium thioglycolate for the mercurial compounds, can be developed. Iodine, when properly employed, would seem to be a valuable agent for skin preparation. Zephiran appears to show considerable promise for numerous uses as a disinfectant. It should be more widely tested, however, in order that its true values and limitations be thoroughly understood.

SUMMARY AND CONCLUSIONS

A number of mercurial disinfectants, which are commonly employed for skin preparation and for the cold "sterilization" of instruments, were tested for their relative bacteriostatic and bactericidal powers against *Staph. aureus* and *E. coli*. All mercurials tested were shown to have relatively high bacteriostatic abilities but low bactericidal powers. Aqueous iodine and zephiran, on the other hand, appeared to be highly bactericidal as well as bacteriostatic.

Certain properties and uses of aqueous iodine and zephiran are further discussed.

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THE USE OF TANTALUM CLIPS FOR HEMOSTASIS IN NEUROSURGERY

ROBERT H. PUDENZ, M.D., MONTREAL, QUE.

(From the Department of Neurology and Neurosurgery of McGill University and the Montreal Neurological Institute.)

THE introduction of the silver clip by Harvey Cushing,[4] in 1911, was a notable advance toward the solution of the problem of hemostasis in neurosurgery. Cushing's original silver clip outfit was considerably improved by McKenzie[7] who changed from the round to a flattened silver ribbon and designed more efficient instruments for cutting, holding, and applying the clips. Penfield[8] designed a smaller clip for use with the McKenzie apparatus (Fig. 1).* This small clip is sizable enough for the control of bleeding from most cerebral vessels and, in addition, is admirably suited for neurosurgical procedures on experimental animals. As a result of the experiments described in this communication, we believe that a further change in the clip is justified, namely, the replacement of silver by tantalum.

The disadvantage of the silver clip lies not in its mechanical properties, but in the extensive inflammatory reaction which it produces in the surrounding tissues. This is a matter of common experience among neurosurgeons and neuropathologists. It has been repeatedly disclosed at a subsequent craniotomy or necropsy. Because of this reaction many neurosurgeons limit their use of silver clips, employing them only when other methods of hemostasis will not suffice.

It is surprising that reports of surgical complications attributable to silver clips are almost nonexistent in the literature. Thorner and Groff[10] have described a case of bilateral lumbar posterior root irritation by migrating silver clips, which occurred four months after a negative suboccipital exploration for tumor. The presence of the clips at the points of emergence of the involved roots was confirmed by roentgenography. It is not unlikely that other complications have occurred but have been either unrecognized or unrecorded.

The neurosurgical staff of this hospital has long been interested in the development of an inert metal from which the Cushing clip could be fabricated. Several metals in current surgical use have been considered. Principal among these inert metals, in addition to tantalum, are vitallium and the several types of stainless steel.

Vitallium is an alloy containing 65 per cent cobalt, 30 per cent chromium, and 5 per cent molybdenum. The widespread use of this metal in surgery is attributable to the original and encouraging experimental findings of Venable, Stuck, and Beach.[11] Screws, nails, and

*As manufactured by the J. F. Hartz Co., Limited, of Montreal and Toronto, under Dr. McKenzie's supervision.

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plates of this material are routinely used by many surgeons in the open treatment of fractures. In addition, vitallium cups have been successfully employed for arthroplasty of the hip by Smith-Petersen.[9] Geib[5] has recently reported the satisfactory repair of cranial defects with this metal.

The orthopedic scope of the stainless steels is essentially similar to that of vitallium. These metals have a further surgical value as suture materials. Their popularity for this latter purpose is due largely to Babcock.[1]

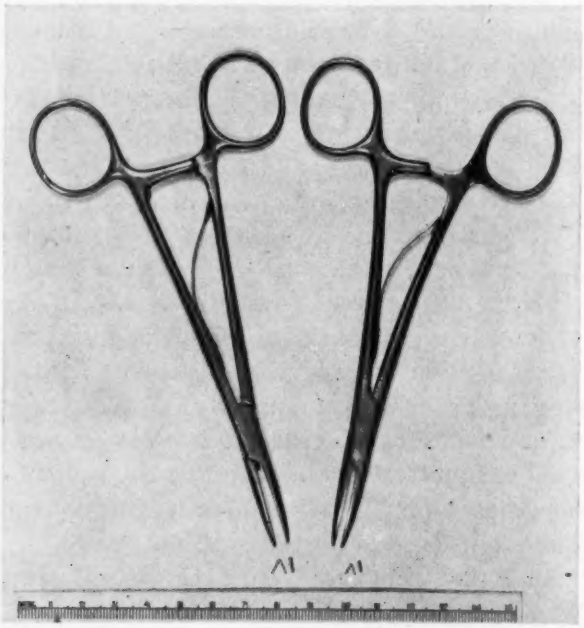

Fig. 1.—Forceps and clips for use with the McKenzie apparatus; Penfield's smaller modification is shown at the right.

Certain inconsistencies of results with these stainless steels have been attributed to variations of chemical composition. The alloy most extensively employed at the present time is the 18/8 type, so-called because it contains 18 to 20 per cent chromium and 8 to 10 per cent nickel. Key[6] has recently introduced enduro, another variety of stainless steel. This alloy contains 16 to 20 per cent chromium, a maximum of 14 per cent nickel, and 2 to 4 per cent molybdenum. He has found experimentally that this alloy is more resistant to corrosion than the 18/8 type.

Unfortunately, vitallium is not adaptable for use in the McKenzie type of clip outfit. Vitallium appliances are made by casting. The alloy cannot be drawn into wire or rolled. It is, therefore, impractical for the manufacture of a thin ribbon from which hemostatic clips could be cut. In contrast, the various types of stainless steel can be cold rolled, drawn into wire, and tempered to varying degrees of hardness. Stainless steel surgical wire does not have the dead-soft

anneal comparable to silver in its plasticity. However, the use of these alloys for the Cushing clip is a matter for further investigation.

The difficulties associated with the search for a metal having the plastic mechanical properties of silver and, in addition, the quality of inertness in the tissues, have been obviated since the recent introduction of tantalum.

In contrast to vitallium and the stainless steels, tantalum is not an alloy but an element, the seventy-third in the periodic table. It was discovered in 1802, by Ekeberg, who so named it because of his "tantalizing" experiences on attempting to dissolve the metal in mineral acids. Physically it is a blue-gray, heavy, malleable, and ductile metal. Chemically it approaches glass in its resistance to acids. Only hydrofluoric and sulfuric acids will attack it. While resistant to weak alkalies, it is destroyed by boiling alkalies and the salts which hydrolyze to form strong alkalies.

Theoretically, these characteristics allow the conclusion that tantalum would be inert in the physicochemical environment of animal tissue. That this is actually so has been shown by the researches of Burch and Carney[2] and Burke.[3] These observers have used tantalum sutures, bone plates, and screws in both animal and human tissues. In none of their subsequent exposures was there evidence of tissue irritation or corrosion of the metal. The screws became so firmly embedded in the bone that they were removed with difficulty. Burke reports that in his series of thirty-four patients, in whom tantalum was used for skin closure, there was a striking absence of scar tissue at the site of skin penetration.

The encouraging results obtained by these observers led to this experimental comparison of the reaction provoked by tantalum and silver in the brain and meninges of animals. In view of the short periods of observation, the report may be criticized as being premature. Nevertheless, it is hoped that the encouraging results obtained in these experiments will stimulate further investigation of the surgical value of this metal.

EXPERIMENTAL COMPARISON OF TANTALUM AND SILVER CLIPS

Adult cats, anesthetized with intraperitoneal nembutal in doses of 40 mg. per kilogram, were used for the experiments. Under aseptic conditions the cerebral hemispheres were exposed bilaterally through single trephine openings. The dura was incised in a cruciate manner and the leptomeninges perforated with the point of a scalpel at the proposed site of insertion of the metallic strips.

Strips of tantalum and silver ribbon, identical in all dimensions, were used. These strips were 0.75 inch in length, 0.030 inch in width, and 0.020 inch in thickness. Each strip was angulated 90 degrees to an "L" shape resulting in a longer and shorter arm measuring 0.5 and 0.25 inch respectively.

The longer arms of these angulated strips were inserted perpendicularly into the cerebral hemisphere, the shorter arm lying in contact with the pia-arachnoid (Fig. 2). The tantalum strips were placed in the right, the silver in the left, cerebral hemispheres. The dural flaps were replaced but not sutured. The temporalis muscles, galea, and skin were approximated with interrupted sutures of black silk and a dry dressing was applied.

Fig. 2.—Diagrammatic cross section of brain showing position of tantalum (*T*) and silver (*S*) strips; the shorter arm of the strip rests on the pia-arachnoid while the longer arm extends into the depths of the cerebral hemisphere.

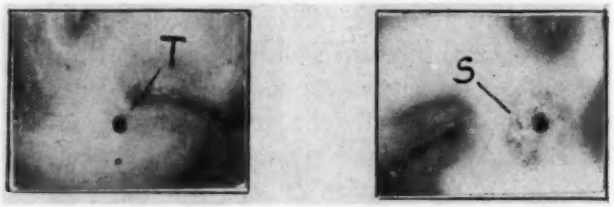

Fig. 3.—Tracts of the tantalum (*T*) and silver (*S*) ribbons in the right and left frontal lobes after eleven days. The area of reaction around the silver strip is obvious (magnification ×4).

Eleven cats were used for this study. The animals were killed at intervals varying from 10 to 148 days. Prior to removal, the brain was fixed in situ by internal carotid perfusion with animal Ringer's solution followed by 10 per cent formalin. The removed brain, with dura intact, was placed in 10 per cent formalin.

When properly hardened the dura was reflected from the cortical surface and the site of strip implantation examined for reaction. Following this inspection the strips were carefully withdrawn from the brain. Blocks of cerebral tissue for microscopic study were cut in a plane allowing examination of the tract of the metal in cross section. These blocks were further hardened in 10 per cent formalin, embedded in paraffin and sectioned at 10 μ. The sections were stained by the hematoxylin and Van Gieson, the Mallory phosphotungstic acid hematoxylin, the Cajal gold chloride sublimate, and the Hortega silver carbonate methods.

RESULTS

Gross Findings.—The meningeal arm of the silver clip was invariably embedded in a mass of tough, pearly tissue. The thickness of this

capsule was greater in the later stages following implantation. It was firmly bound to the overlying dura. The extracted silver clip had a brownish-black discoloration of its surface. Finally, on cutting the tract of the clip in cross section, a marginal zone of greenish softening, at times 3 mm. in diameter, was noted (Fig. 3).

In contrast, the tantalum ribbon provoked but minimal reaction. Encapsulation of the meningeal segment was at most a delicate, translucent membrane continuous with the leptomeninges. Meningocerebral adhesions at the site of insertion were few and fragile. The blue-gray luster of the metal was unchanged. The tract, as seen in cross section, was sharply outlined. Reaction in the surrounding brain was indiscernible with the naked eye (Fig. 3).

Fig. 4A.—Reaction surrounding silver clip thirty days after implantation. Note the large masses of polymorphonuclear leucocytes within the tract (*T*), the secondary zone (*S*) of glial, vascular, and connective tissue response and the extension of the reaction into the leptomeninges of an adjacent sulcus (*M*).

Microscopic Findings.—The gross impression of the intensity of the reaction surrounding the silver clip was confirmed by microscopic examination. For practical purposes this reaction is divisible into proximal and distal zones. In the early stages the proximal zone consisted of a wide collar of polymorphonuclear leucocytes. Later many of these cells showed degenerative changes with small round cells and phagocytes filled with brown-black pigment granules dispersed among them. Surrounding this area of compact cells was the distal zone in which chromatolysis of ganglion cells, amoeboid types of microglia, gliosis, and the proliferation of blood vessels were noted. The term "gliosis" is used broadly to indicate the proliferation and hypertrophy of astrocytes with the laying down of neuroglia fibrils. Collections of small round cells and compound granular corpuscles were found around the vessels. Most striking in this distal zone was the large number of fibroblasts.

These cells eventually formed a thick sheath of collagenous connective tissue around the metal. These proximal and distal zones of reaction are evident in Fig. 4, *A*. In this instance the inflammatory cells have extended into the leptomeninges of an adjacent sulcus.

Examination of the brain bordering the tantalum tract disclosed but slight reaction to this metal. Mobilization of inflammatory cells and the proliferation of fibroblasts and vessels were minimal. At the end of 148 days the strip was invested in a thin collagen sheath bordered by a narrow zone of astrocytic proliferation and hypertrophy. In a few instances compound granular corpuscles filled with blood pigment were noted in the tract. The presence of these cells was undoubtedly the result of hemorrhage concurrent with insertion of the strips. In one experiment, where the strip lay partly within a sulcus, the meningeal component of the tract consisted of a narrow, collagenous band while the cerebral component was the usual neuroglial brushwork. The characteristic reaction to tantalum is shown in Fig. 4, *B*.

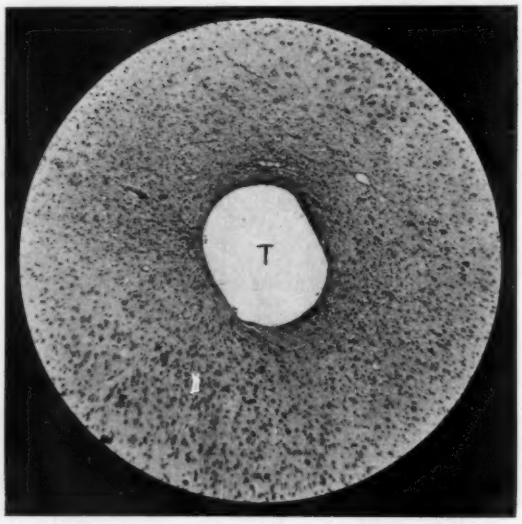

Fig. 4*B*.—Cross section of tract (*T*) occupied by tantalum for thirty days; note the slight marginal gliosis and the lack of inflammatory reaction.

DISCUSSION

These findings offer additional evidence that tantalum does not irritate tissues. In all of the experiments the reaction to the metal, when in contact with the meninges or nervous tissue, was a minimal encapsulation by fibroblasts and/or neuroglia fibrils, depending on the location. In contrast, silver has invariably provoked an intense inflammatory reaction, leading ultimately to investment in dense collagenous connective tissue. The character of this tissue reaction to silver is not unlike that of cerebral abscess formation.

In view of the intensity of the reaction to silver, we are convinced that the replacement of this metal by tantalum is a considerable

refinement in technique. Large and small tantalum hemostatic clips for use in the McKenzie clip forceps are now in routine use in our operating theatres. The large clips are cut from dead-soft annealed tantalum ribbon 0.028 inch wide by 0.014 inch thick, and the small clips from a ribbon 0.020 inch wide by 0.010 inch thick. These ribbons are narrower in both dimensions than the standard silver ribbons and are not knurled. The tantalum clips are similar to silver clips in plasticity and permit a firm grasp on the site of hemorrhage.

Further studies of the neurosurgical value of tantalum are now in progress. The metal has been used in the form of a foil to protect cerebral wounds from the ingrowth of dural fibrous tissue and tantalum sheet of varying thickness has been employed to obliterate bony defects in the skull. The results of these experiments will be published in a later communication.

SUMMARY AND CONCLUSIONS

1. The reactions provoked by silver and by tantalum ribbon when implanted in the brains and meninges of cats for periods of time varying from 10 to 148 days are reported.

2. The silver clip provokes an intense inflammatory reaction in both nervous tissue and meninges, leading eventually to dense encapsulation.

3. The reaction to tantalum consists of a minimal investment by connective tissue and/or neuroglia fibrils. The characteristic foreign body reaction is not found.

4. The conclusion drawn from this evidence is that the tantalum clip should replace the silver clip for hemostasis in neurosurgical procedures. This is particularly true in cases where irritation leading to focal epilepsy may be feared as a late complication of operation.

The tantalum ribbon used in these experiments was supplied through the courtesy of the Fansteel Metallurgical Corporation of North Chicago, Ill.

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Editorial

Acute Perforated Gastroduodenal Ulceration

PROBABLY the most frequent and the most serious complication of gastroduodenal ulceration is acute perforation. On the basis of large statistical studies it has been estimated that from 10 to 15 per cent of all "peptic" ulcers perforate and that from 20 to 25 per cent of all patients with perforated ulcer die. Even more significant is the fact that this complication is apparently increasing. Moreover, it would not be hazardous to predict that with the present wide-flung conflict there will be an even greater increase in the incidence of acute perforation. The cause of this increase has not been explained satisfactorily but a number of psychic and physical factors are believed to be contributory. Included among these are economic strain, poor nutrition, accelerated mental and physical activities, excessive smoking and imbibition of alcoholic beverages, and, particularly in soldiers, nostalgia, mental depression, and other emotional stresses. Accordingly, if these factors play significant roles in the development of gastroduodenal ulceration, and there is good reason to believe that they do, current military operations on such a prodigious scale will undoubtedly be associated with an even greater increase in the incidence of this serious complication.

There are a number of other interesting features of acute gastroduodenal perforation that are not thoroughly understood. Thus, it has long been known that from 90 to 95 per cent of these complications occur in males, and almost three-fourths of the patients are between the ages of twenty and fifty years. The possibility of a "protective" or hormonal factor obviously suggests itself as an explanation for the sexual predominance but in spite of isolated studies this remains in the intriguing speculative phase. Similarly, the relative immunity in individuals under twenty years of age remains conjectural. Whereas some significance has been attributed to a racial factor, careful observers have shown that this condition occurs with almost equal frequency among Caucasian, Negroid, and Asiatic races. Similarly, the existence of a seasonal influence remains disputative. The etiologic significance of occupation in perforated ulcer also is not clear. Whereas it is commonly believed that the high tensioned, energetic executive is the most liable candidate for this complication, extensive statistical analyses have shown that the laboring classes comprise the largest number.

Another intriguing question is: Why do ulcers perforate? This is obviously difficult to answer because the etiology of gastroduodenal

ulceration is still unestablished. However, it poses as an interesting speculative problem. We have previously expressed the belief that all patients with gastroduodenal ulceration are potential candidates for perforation but only those ulcers perforate which are exposed to certain precipitating "perforative" factors. These consist essentially of trauma, infection, and a local lack of tissue resistance.

There are still other interesting, controversial, and incompletely understood problems in the pathology, bacteriology, clinical manifestations, and diagnosis of perforated gastroduodenal ulceration but their consideration here would be inopportune and inexpedient. More pertinent are the prognostic and therapeutic considerations. Thus, although the mortality in this condition has steadily decreased during the first three decades of the present century, it has diminished almost insignificantly during the last decade. This poor reflection of considered improvement in diagnostic methods, preoperative and postoperative therapy, anesthesia, and surgical technique clearly emphasizes the necessity for a more intensive consideration of this subject.

There are a number of prognostically influential factors in this complication. Among the most important of these are sex, age, location of the lesion, time elapsing between perforation and treatment, type of anesthetic employed, and development of complications. It is an interesting and unsatisfactorily explained fact that the mortality in females is almost twice that in males. More readily explicable is the significance of the age factor, which is shown by the fact that in patients under 40 years of age the mortality is less than 20 per cent, whereas in those over 40 years there is a commensurate increase in mortality from 30 to 50 per cent. The prognostic significance of the site of perforation is demonstrated by the fact that the mortality is from 10 to 15 per cent greater in gastric than in duodenal perforations. This has been explained on the basis that the former are more liable to occur in older patients and are more liable to be associated with greater spillage of intragastric contents into the peritoneal cavity. It has long been common knowledge that the mortality in perforated ulcer is almost directly proportional to the time elapsing between the perforation and the operation, that is, the longer this period the greater the mortality. This is clearly demonstrated by the fact that in an analysis of more than 7,000 cases, the mortality in those treated during the first six postperforative hours was about 10 per cent, whereas in the second six-hour period the mortality doubled, in the third quadrupled, and in the fourth had increased sixfold. Although the importance of anesthesia is somewhat controversial, the majority of recent observers consider spinal analgesia the most desirable. The fact that the mortality following spinal analgesia was approximately one-half that following general anesthesia in a large collected series clearly emphasized its significance. We have previously expressed the opinion that the former is preferable because complete relaxation is obtained, permit-

ting better exposure and less manipulative trauma, and because the toxicity of the latter is an additional burden upon the liver.

Although all are agreed that the treatment of acute perforated gastroduodenal ulceration is surgical, there is considerable controversy regarding the procedure of choice; the majority of American and English surgeons favor the more conservative procedure of simple closure and the continental European surgeons warmly advocate the more radical procedure of partial gastrectomy. Between these two extremes lie the advocates of closure plus gastroenterostomy and excision plus closure or pyloroplasty. The attempt to determine the superiority of these respective procedures by the comparative mortality rates is fallacious because numerous other factors such as those already mentioned, as well as the personal equation of the skill and experience of the surgeon, influence the mortality. Indeed, such a statistical study revealed that the mortality following the more conservative procedure of simple closure was not only the highest but twice as great as that following the more radical procedure of gastrectomy. This obvious discrepancy with well-established surgical principles clearly emphasizes the importance of other factors. That the various procedures advocated have their respective advantages, disadvantages, and indications is readily admitted and has been comprehensively reviewed in a previous publication. However, on the basis of surgical rationale, it is our firm conviction that the procedure of choice in the majority of cases is the one which effects most expeditiously adequate repair of the defect. Accordingly, the procedure of simple closure is considered the most desirable. Reinforcement with an omental graft is of additional value. Of interest in this connection and for the sake of recorded accuracy it should be realized that the use of an omental plug was suggested in 1896 by Bennett. The procedure of added gastroenterostomy in the majority of cases is considered not only unnecessary and "meddlesome" surgery but also hazardous because of the subsequent development of an anastomotic jejunal ulcer. Whereas the reported incidence of this serious complication varies from less than 5 to over 50 per cent, depending upon the care and thoroughness of the follow-up studies, we are convinced that it occurs with sufficient frequency and associated danger to justify its condemnation. In fact, its one occasional justification, pyloric constriction, may be combated better by some form of pyloroplasty.

Michael DeBakey, M.D.
New Orleans, La.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE PHYSIOLOGY OF PLASMA PROTHROMBIN AND ITS RELATION TO LIVER FUNCTION*

WILLIAM DEW. ANDRUS, M.D., AND JERE W. LORD, JR., M.D.
NEW YORK, N. Y.
(From the Department of Surgery of the New York Hospital and Cornell University Medical College)

INTRODUCTION

THE consideration of the plasma prothrombin in modern surgery had its inception approximately ten years ago when Lewisohn,[1] while studying the clotting mechanism in the hemorrhagic tendency associated with jaundice, found that the level of plasma prothrombin was reduced. However, the direct connection between lowered levels of plasma prothrombin and the hemorrhagic tendency associated with jaundice was not appreciated until 1935, when Quick, Stanley-Brown, and Bancroft[2] observed a definite relationship between the occurrence of hemorrhage and lowered levels of plasma prothrombin as indicated by a satisfactory test devised by Quick.[3, 4] The use of this test and others, in particular the titration method of Warner, Brinkhous and Smith,[5] has added much to our knowledge of the physiology of plasma prothrombin, including the establishment of the site of its formation and loss, its fluctuations in a variety of physiologic and pathologic states, and its relation to vitamin K.

It was early established that the liver is intimately related to plasma prothrombin, and as further information accumulated various workers have utilized the level of activity of this substance as a measure of hepatic function.

NATURE OF PLASMA PROTHROMBIN

A. *Chemical Studies.*—Brinkhous[6] recently described the following characteristics of plasma prothrombin. It is associated with the pseudoglobulin fraction of the plasma protein, is salted out of plasma between one-third and one-half saturation with ammonium sulphate and at pH 5.3 is largely precipitated from diluted plasma. Prothrombin is also precipitated by adding acetone to plasma and is nondialyzable through collodion and cellophane. It is adsorbed on a number of colloidal preparations, including calcium phosphate, magnesium hydroxide, aluminum

*This study was carried out under a grant from the John and Mary R. Markle Foundation.

hydroxide, and colloidal starch, as well as by passing plasma through a Seitz filter. It is thermolabile, being destroyed by heating plasma for one-half hour at 56° C. Preservation of plasma at room temperature leads to fairly rapid disintegration of prothrombin, whereas plasma in the frozen state maintains its prothrombin activity for weeks. Biologically potent but chemically crude preparations of prothrombin have been prepared by Mellanby,[7] and by Seegers, Smith, Warner, and Brinkhous,[8] by precipitation from dilute plasma at pH 5.3 and adsorption on magnesium hydroxide. It is then separated from the adsorbing agent by carbon dioxide and dialyzed against water to remove a number of insoluble impurities. After evaporation the resultant dry powder is water soluble, and contains approximately 150 units of prothrombin per milligram. Brinkhous adds that a more recent preparation of prothrombin by modification of the above method has yielded a substance having a potency of 500 units per mgm.

B. *Biologic Activity.*—Although the exact chemical nature of prothrombin remains an unsolved mystery, its biologic activity has been established during the past seven years, as involved in the clotting mechanism as follows:

1. Prothrombin + calcium + thromboplastin → thrombin
2. Thrombin + fibrinogen → fibrin (clot)

Eagle[9] concludes that calcium and thromboplastin are catalysts which speed the conversion of the prothrombin to thrombin and that thrombin is likewise a catalytic agent which activates the transformation of fibrinogen to fibrin reaction. In Eagle's studies on snake venom and various enzymes such as trypsin, the basic two stages could be carried out without calcium and thromboplastin in the first process and thrombin in the second process. However, Mertz, Seegers, and Smith[10] believe that thromboplastin is not an enzyme but rather that it takes part in the reaction and therefore suggest that the first stage is a direct chemical interaction in which both thromboplastin and prothrombin are consumed.

C. *Tests for Plasma Prothrombin.*—Tests for plasma prothrombin merely assay its capacity to form thrombin and its activity is assumed to parallel the amount present.

Quick's test[3, 4] is a one-stage technique for measuring the clotting time of oxalated plasma after the addition of an excess of thromboplastin and a relatively optimal amount of calcium. The assumptions are made that the fibrinogen is normal and that the clotting time which ensues represents the amount of prothrombin present. Actually, two temporal components exist, the time for the conversion of prothrombin to thrombin, and the time it takes the thrombin to act on the fibrinogen.

The Warner, Brinkhous, and Smith[5] test, on the other hand, is a two-stage technique which allows for the conversion of the prothrombin

to thrombin and then with a fixed amount of fibrinogen, calcium, and thromboplastin the time required for the clot to occur is determined. The amount of thrombin formed is equivalent to the quantity of prothrombin present and the solution is diluted so that when the second stage is carried out a clot will form in fifteen seconds. A unit of thrombin is defined as the quantity which, under standard conditions, will cause clotting of 1 c.c. of a fibrinogen solution in fifteen seconds. One unit of prothrombin is the amount required to form one unit of thrombin. By this test, human plasma contains approximately 300 units of prothrombin per c.c.

Allen, Julian, and Dragstedt[11] described a modification of the Quick test which is more sensitive in the detection of hypoprothrombinemic states and more accurately depicts the response in the plasma prothrombin to therapy with vitamin K. Their modification consists in the serial dilution of the plasma, to concentrations ranging from fifty to five per cent of the original undiluted plasma. The authors used thromboplastin made from lung extract, and normal human plasma as a control with each group of unknowns.

More recently Ziffren, Owen, Hoffman, and Smith[12] described a so-called "bedside test" for prothrombin activity in which freshly drawn whole blood is mixed with a fixed amount of thromboplastin and the clotting time determined. All patients are checked with a control and the result is expressed in per cent of normal. The authors have found that for practical purposes there is a fairly close parallel between the level of plasma prothrombin as determined by the "bedside test" and the two-stage titration technique.

Kato[13] in 1940 described a microprothrombin test which is a modification of Quick's test and in which oxalated whole capillary blood is used instead of larger amounts of venous plasma. It requires only 10 c.mm. of whole blood, and hence has great applicability in studies of plasma prothrombin in infants.

Ferguson, Calder, and Reinhold[14] compared Quick's test with the serum volume test of Boyce and McFetridge[15] and with the bleeding time of Ivy[16] on a group of patients and found that the latter two tests used in conjunction never failed to detect a potential or actual bleeder due to prothrombin deficiency.

SOURCE OF PLASMA PROTHROMBIN

A. *Experimental Studies.*—Earlier speculation had suggested the bone marrow as the source of plasma prothrombin.[17] Barnes,[18] however, demonstrated in laboratory animals (mouse, rat, rabbit, and dog) that depression of the bone marrow by large doses of roentgen rays in acute experiments, as well as by protracted courses of small doses of x-ray, had no effect on the level of the plasma prothrombin. The true

site of its formation was indicated by Smith, Warner, and Brinkhous[19] who, using chloroform as the hepatotoxin, observed a precipitous fall in plasma prothrombin to less than 10 per cent within twenty-four hours, and a return to normal only after six days had elapsed. Quick[4] made similar observations on the dog, with chloroform anesthesia.

Warner,[20] after removing approximately 65 per cent of the liver of the rat, demonstrated a fall in plasma prothrombin which returned to normal in about two and one-half weeks. Andrus, Lord, and Moore,[21] and Warren and Rhoads[22] independently performed total hepatectomy in dogs and found that the plasma prothrombin fell progressively to lower levels. The former workers also demonstrated that the administration of vitamin K in large amounts failed to alter this rate of fall, indicating that the liver is the chief, if indeed it is not the sole site of prothrombin formation. Recently, Brinkhous and Warner[23] found that the plasma prothrombin depressed by chloroform poisoning failed to respond to vitamin K therapy.

Bollman, Butt, and Snell[24] produced chronic hepatic injury in the rat with carbon tetrachloride vapor and were able to demonstrate depression of the plasma prothrombin level and failure of vitamin K to influence it. These authors also observed that a high carbohydrate diet delayed the onset of hepatic damage and prolonged the lives of the animals by as much as 50 per cent.

B. *Clinical Studies.*—Many observers during the past four years have stressed the fact that in the presence of hepatic disease the plasma prothrombin not only is depressed but also fails to respond adequately to vitamin K therapy. Quick,[4] Butt, Snell, and Osterberg,[25] Brinkhous, Smith, and Warner,[26] Stewart and Rourke,[27] Rhoads,[28] Lucia and Aggeler,[29] Pohle and Stewart,[30] Allen and Julian,[31] and Andrus and Lord[32] reported cases in which poor response was obtained and attributed this to liver damage.

Although there is some variation in the above authors' opinions as to the exact types of hepatic disease in which the plasma prothrombin fails to respond to the administration of vitamin K, there is general agreement that vitamin K therapy is adversely influenced by the presence of hepatic damage and that improvement in hepatic function is usually associated with a rise in the plasma prothrombin.

DESTRUCTION OF PLASMA PROTHROMBIN

Andrus, Lord, and Kauer[33] have pointed out that plasma prothrombin is being continuously lost from the blood as it circulates through the lungs. In a series of twenty experiments the prothrombin activity was found to be less in the blood of the left ventricle than in that from the right ventricle in seventeen. This difference averaged 10.6 per cent and ranged from 4 to 19 per cent. In no instance was the level in the

right ventricle lower than that in the left. In samples of blood taken from the arterial and venous supply of the head, liver, spleen, intestine, kidneys, and lower limbs no significant difference in plasma prothrombin levels was found. A possible explanation of this role of the lung in the loss of plasma prothrombin was thought to be the production of blood platelets in this organ. Platelets, as they undergo disintegration, initiate the first stage of the clotting process by releasing thromboplastin, which, in the presence of calcium, changes prothrombin to thrombin.

The importance of the above finding is to substantiate further the fact that plasma prothrombin is biologically a highly labile substance and any injury to the liver, its source, is followed by a fall in the amount in circulation in a very short period of time.

TESTS OF LIVER FUNCTION

A. *Plasma Prothrombin as an Index of Hepatic Function.*—The vital role played by the liver in the formation of prothrombin and the rapidity with which the level of this substance falls after experimental liver injury or hepatectomy suggest the possibility of following the level of the plasma prothrombin as an index of liver function. Pohle and Stewart[30] in 1940, were the first to publish a report of clinical experience with such a test, suggesting specifically that the response of a depressed plasma prothrombin level as measured by the Quick test, to vitamin K and bile salts administered by mouth, might be a satisfactory means of indicating liver function. In their series of 46 jaundiced patients with reduced plasma prothrombin, 28 showed a satisfactory response, while in 18 there was no improvement. Wilson (34) also suggested that the level of the plasma prothrombin might be considered as an index of hepatic function, and in a series of 36 patients found a close correlation between the level per se and the results of hippuric acid tests.

The use of the level of the plasma prothrombin alone as a measure of liver function is open to serious objection, however, since it may be depressed by dietary or other factors in the absence of liver damage.

Since October, 1939, we have studied the application of the level of plasma prothrombin and its response to intramuscular 2-methyl-1, 4-naphthoquinone as a measure of liver function in some eighty-six cases, and within certain restrictions find it perhaps the most accurate method available. We prefer the parenteral route, intramuscular in all our own cases, for the reason that we have encountered at least two otherwise normal individuals in whom, despite the presence of bile in the intestine and apparently normal liver function by several tests, the plasma prothrombin was depressed to about 60 per cent of normal and could not be elevated by vitamin K administered by mouth with or without bile salts. Intramuscular injection was followed by a prompt elevation to normal. This we can only explain by postulating a defective absorption from the intestinal tract.

We therefore have adopted the thesis, which is well borne out by clinical data to be presented below, that the level of the plasma prothrombin if below 80 per cent in a given case, is an index of the performance of the liver, while the response to 2 mg. of 2-methyl-1, 4-naphthoquinone administered intramuscularly indicates whether any depression of this function is or is not due to organic liver disease.

B. *Comparison of Tests for Hepatic Function.*—During the past four years a large number of tests of hepatic function have been studied by a variety of workers and as a result have attained a useful place in the study of patients. The hippuric acid test, the galactose tolerance, bromsulphalein excretion, and Hanger's cephalin-cholesterol flocculation tests seem to be the outstanding ones in use at present.

The hippuric acid excretion test has been found of value in the preoperative evaluation of the surgical patient by Boyce and McFetridge,[35] and they have made use of the test in hyperthyroidism as have Bartels[36] and Haines, Magath and Power.[37] The consensus of opinion is that while the test cannot supplant clinical judgment in estimating the danger of thyroidectomy to the patient or in indicating the length of time preoperative preparation should be continued, it does emphasize that the liver is intimately concerned in the metabolic derangement of the patient with hyperthyroidism and may be involved in the production of the symptom of postoperative thyroid crisis.

Quick[38] advocates the hippuric acid test as a useful means of differentiating intrahepatic and extrahepatic jaundice, but Snell and Plunkett[39] concluded that the test was of less aid in the differentiation of the two types of jaundice, although they did consider it more satisfactory than the galactose tolerance and bromsulphalein excretion tests in the estimation of the degree of hepatic damage.

During the past two years several reports have been made on the comparison of the plasma prothrombin and the other liver function tests mentioned above, with the exception of the cephalin-cholesterol flocculation test.

Wilson[40] found in nonjaundiced patients with a wide variety of diseases of the liver, a close correlation between the level of the plasma prothrombin as measured by the two-stage titration test of Warner, Brinkhous, and Smith[5] and the hippuric acid test described by Quick.[38] On the other hand, Lucia and Aggeler[29] concluded that there was no significant correlation between the two tests although they felt that the response of the plasma prothrombin to vitamin K reflects the state of the liver in a variety of diseases of the liver and biliary tract. These workers drew their conclusions from prothrombin determinations by the method of Quick,[3] but as Wilson[40] pointed out, the margin of error in the Quick test is rather too large for such exact estimations. We agree with Lucia and Aggeler that the response of the plasma prothrombin to

vitamin K therapy is a better measure of liver function than the level of the prothrombin because of the relative frequency of conditions such as sprue, ulcerative colitis, etc., in which hepatic function is normal but the absorption of the vitamin is defective. We also agree with Wilson that the two-stage prothrombin test is essential in the exact determination of hepatic function and comparison with other tests. Kark, White, Souter, and Deutsch,[41] using the Quick test for plasma prothrombin, found no significant correlation between the hippuric acid test and the response of the plasma prothrombin to synthetic vitamin K analogues. DeLor and Reinhart,[42] comparing the plasma prothrombin as determined by the Quick test, bromsulphalein excretion, galactose tolerance, and hippuric acid tests, concluded that the bromsulphalein test is the most sensitive one of their series for the identification of early liver damage, and consider the galactose tolerance test the least reliable of the group. In all cases in which the hippuric acid excretion was below 2.0 Gm., the plasma prothrombin was reduced, while in the group whose excretion of hippuric acid was between 2.0 and 3.0 Gm., the plasma prothrombin was normal in 87 per cent of the cases.

Andrus and Lord[43] have employed the response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as determined by the Warner, Brinkhous, and Smith test as a measure of hepatic function and have compared the test with the galactose tolerance, hippuric acid, and bromsulphalein clearance tests in three groups of selected patients. In a group of seven patients with Laënnec's type of cirrhosis of the liver the plasma prothrombin failed to rise by more than 6 per cent after the intramuscular injection of 2 mg. of menadione. This failure to respond, we feel, indicates intrahepatic disease of a significant degree, but prognosis is only possible when the test is employed on several occasions and the trend observed. The galactose tolerance test was used in six of the seven patients with cirrhosis of the liver and results were abnormal in only four. The hippuric acid test was less accurate than the galactose tolerance test, being below 100 per cent (3 Gm.) in only two out of five of the cases. The bromsulphalein test stood last in point of accuracy with three normal results in three cases of cirrhosis.

In a group of nine cases of catarrhal jaundice the plasma prothrombin test showed impaired hepatic function in seven instances and in general paralleled the severity of the disease. The galactose tolerance test was equally accurate in this group, showing greater than 3 Gm. excreted in seven out of nine patients. The results in the hippuric acid test were abnormal in three out of seven cases, while those in the bromsulphalein test were abnormal in only two out of five instances. Interestingly, the bromsulphalein test gave abnormal results (10 per cent retained) in one case of catarrhal jaundice proved at operation, in which the results of the other three tests were normal.

The third group of patients studied suffered from obstructive (extrahepatic) jaundice due to a variety of lesions. The plasma prothrombin response was good in all of eleven cases in which it was used, while the galactose tolerance test was normal in only six out of nine cases. The hippuric acid test was normal in seven out of eight and the bromsulphalein test was normal in all four cases in which it was used. In this group of patients with extrahepatic jaundice the question arises as to whether the impairment of hepatic function as determined by the galactose tolerance test is significant or not. If significant, then the plasma prothrombin test is less sensitive in this group than the galactose tolerance test. It seems clear that the bromsulphalein test was the least sensitive in each of the three groups of cases and that the plasma prothrombin is the most accurate, with the galactose tolerance test a close second. The hippuric acid test falls between the galactose tolerance and the bromsulphalein tests in point of accuracy.

TABLE I

COMPARATIVE RESULTS OF LIVER FUNCTION TESTS SHOWING GREATEST IMPAIRMENT 24 TO 48 HOURS AFTER MINIMAL DOSES OF CHLOROFORM

CHLOROFORM (C.C. PER KG.)	DOG NUMBER	PLASMA PROTHROMBIN PER CENT OF NORMAL (NORMAL = 100%)	BROMSULPHALEIN PER CENT RETAINED (NORMAL = 0-10%)	GALACTOSE TOLERANCE GRAMS EXCRETED (NORMAL = < 3.0 GM.)
	1	70	0	
0.03	2	69	7	
	3	62	0	
	4	75	0	
0.06	5	58	0	
0.09	6	60	0	
0.10	7	< 8	10	
	8	< 6	25	
0.12	9	< 3		2.9
	10	54		1.5
0.18	11	< 2		3.3
	12	< 3		3.2
0.24	13	< 3		3.9

< = less than.

However, all clinical studies of the comparison of various liver function tests are unsatisfactory because of the difficulty in controlling the many factors which may influence the disease and the patient. Also, diagnosis cannot always be established with certainty without operation or autopsy. Hence, recent work by Andrus and Lord[43] on the use of the injection of minute amounts (0.03 to 0.24 c.c. per kilogram) of chloroform subcutaneously into dogs and comparing the level of the

plasma prothrombin with galactose tolerance and bromsulphalein clearance tests is of interest. They found that the plasma prothrombin fell to 28 per cent of normal in twenty-four hours after the injection of 0.12 c.c. per kilogram of chloroform, while the galactose tolerance test remained normal (less than 3.0 Gm. excreted). When 0.24 c.c. per kilogram of chloroform was injected, the plasma prothrombin fell to less than 3 per cent of normal, while the galactose tolerance test showed an excretion of only 3.6 Gm. in the urine. The bromsulphalein test with 0.03 c.c. per kilogram showed an average retention of 2 per cent in 30 minutes (up to 10 per cent retention is considered to be normal), while the plasma prothrombin fell to an average of 67 per cent. When 0.12 c.c. per kilogram of chloroform was used, the bromsulphalein showed a retention of 25 per cent, while the plasma prothrombin fell to 6 per cent.

It is evident from the above findings that the plasma prothrombin is a far more sensitive index of liver damage in chloroform intoxication than is the bromsulphalein clearance test, and that the latter is considerably more sensitive than the galactose tolerance test.

RELATION OF PLASMA PROTHROMBIN TO SURGICAL DISEASE

As a working hypothesis to be applied in any specific instance, we may look upon the vitamin K-plasma prothrombin relationship in the following way. Into the final formation of plasma prothrombin there enters an extrinsic factor, vitamin K; an intrinsic factor, bile salts; an absorptive mechanism, the intestinal epithelium; and the liver, which not only stores vitamin K but from it elaborates prothrombin.

Any derangement of function or lack of supply of any of the above factors may lead singly or in combination to lowered levels of plasma prothrombin, and hence to the hemorrhagic tendency now known to be associated with a wide range of pathologic states.

A. *Obstructive Jaundice.*—In this condition, whether it be due to carcinoma of the head of the pancreas, stone in the common duct, or some other pathologic abnormality blocking the biliary pathways, the bile is prevented from reaching the intestinal tract, with the result that the absorption of all fat-soluble vitamins, of which K is one, is interfered with. As this continues, the level of the hepatic store of the vitamin falls, and there is a concomitant fall in the plasma prothrombin. Lord, Andrus, and Moore[44] demonstrated by the curative method of assay on chickens that the liver of dogs made vitamin K deficient by exclusion of bile from the intestinal tract (obstructive jaundice or biliary fistula) contains progressively less vitamin K, and that the level of the plasma prothrombin bears a linear relationship to the quantity of the vitamin in the liver. In addition, if the obstruction continues unabated, morphologic changes in the liver occur which are characterized

as obstructive biliary cirrhosis. This state of itself leads to a diminished capacity of the liver to elaborate plasma prothrombin even in the presence of an adequate supply of vitamin K. Hence, the patient with obstructive jaundice is likely to bleed if vitamin K with bile salts, orally, or menadione intramuscularly or intravenously are not administered, and if the disease progresses without relief to such an extent that the hepatic damage is too severe. In the former case therapeutic measures are effective, whereas in the latter all efforts to promote the formation of prothrombin may be in vain.

Before the advent of vitamin K, hemorrhage was the cause of death in approximately 50 per cent of the cases of obstructive jaundice in which patients died following surgical intervention. In contrast to the above findings, since the use of vitamin K there has been not a single death due to hemorrhagic tendency in patients with obstructive jaundice of extrahepatic origin on the surgical service of the New York Hospital.

It has been pointed out repeatedly in clinical studies that the hemorrhagic tendency more often becomes manifest in the postoperative period than at any other time. Stewart, Rourke, and Allen[45] found that the plasma prothrombin fell 15 to 25 per cent during the immediate postoperative period in a group of four patients subjected to operation upon the biliary tract, whereas the fall in the group of five patients without biliary tract disease was observed on only one case and amounted to only 15 per cent. We[46] have confirmed the normal prothrombin levels in patients operated upon for brain lesions, hernioplasties, and major abdominal procedures in whom the liver was not handled. Lord[47] and Cullen and co-workers[48] have demonstrated in the dog that massage of the liver for twenty-five minutes produces a fall of 25 per cent in the level of the plasma prothrombin, from which recovery is made within six days. The latter workers have studied the effect of anesthesia on plasma prothrombin and found that of ether, cyclopropane, and chloroform, only the last produced significantly depressed levels during the postoperative period. Allen and Livingstone[49] studied a variety of anesthetic agents exclusive of chloroform and concluded that the postoperative fall which occurred was not due to the type of anesthetic but rather to the state of the stores of vitamin K, "potential prothrombin," in the body.

With the observation on the depressing effect of operation on the plasma prothrombin outlined above in mind, it would seem unwise to perform an elective operation on any patient with a level of plasma prothrombin below 50 per cent, as the critical bleeding level is 20 to 25 per cent of normal by the Warner, Brinkhous, and Smith test. Hence, allowing 25 per cent for the postoperative fall, there would be no margin for safety unless the plasma prothrombin were 50 per cent of normal or higher preoperatively.

Excellent clinical reports have been made by Smith and co-workers,[50] Butt, Snell, and Osterberg,[25] Dam and Glavind,[51] Rhoads,[52] Quick,[4] Stewart and Rourke,[27] Illingworth,[53] and Allen and Julian.[54]

B. *Biliary Fistula.*—The hemorrhagic tendency may become manifest in patients with a biliary fistula since, as in obstructive jaundice, the absence of bile in the intestine leads to a failure of the absorption of the fat-soluble vitamin K and hence to a diminished level of plasma prothrombin. Experimentally, Hawkins and Whipple[55] and Hawkins and Brinkhous[56] in 1935-1936 demonstrated the hemorrhagic tendency in dogs with biliary fistulae and showed that the bleeding was due to a deficiency of plasma prothrombin. The relation of vitamin K and the level of plasma prothrombin in dogs with biliary fistulae was determined by Smith, Warner, Brinkhous, and Seegers[57] in 1938. In these animals the liver remains normal grossly and microscopically and the fall in plasma prothrombin is more gradual than in the animals with obstructive jaundice, since in the latter the combination of exclusion of bile from the intestinal tract interfering with the absorption of vitamin K, and the mechanical obstruction to the outflow of bile may lead to a secondary hepatic damage in the form of cirrhosis.

Brinkhous, Smith, and Warner[26] in 1938 reported a case of external biliary fistula due to stricture of the common bile duct and observed plasma prothrombin levels of 29 per cent which, after the feeding of whole bile, rose to 89 per cent. There was temporary oozing of blood from the wound on the fourth and fifth postoperative days, which ceased following a blood transfusion. Zuckerman, Kogut, Jacobi and Cohen[58] in 1939 reported an excellent study of the plasma prothrombin and other hematologic findings in a patient with a complete external biliary fistula. The patient was placed on a low fat, vitamin K deficient diet without the administration of bile or bile salts, with the result that the plasma prothrombin time rose from 30 to 150 seconds and the patient bled from the gums, tongue, and vagina. Neither the prothrombin time nor the actual bleeding was altered by the feeding of bile or vitamin K alone, but the prothrombin time returned to normal (twenty seconds) and the bleeding ceased within eight days after the feeding of bile and vitamin K concentrate together. Numerous other workers have reported similar experiences.

C. *Hepatic Disease.*—Concomitantly with the development of the experimental evidence that the liver is the site of elaboration of plasma prothrombin, clinical studies revealed that prothrombin is lowered in a variety of diseases of the liver. Cirrhosis of the liver has been widely recognized to be associated with lowered levels of plasma prothrombin[27, 34, 59, 60] and the failure of the plasma prothrombin to respond to vitamin K has been repeatedly emphasized by Allen and Julian,[31] Stewart,[61] Andrus and Lord,[32] and others. It is interesting to note that

in the authors' experience no case of extrahepatic jaundice has failed to respond to synthetic vitamin K therapy in spite of long-standing jaundice, of six months' duration in one case. On the other hand, only one case of typical cirrhosis has shown an elevation of plasma prothrombin following the injection of similar amounts of the vitamin.

Other types of liver disease such as multiple abscesses of the liver,[4, 62] catarrhal jaundice,[31, 62] and subacute yellow atrophy[63] are associated with depressed levels of plasma prothrombin which fail to respond to vitamin K administration.

D. *Intestinal Disease and Nutritional Deficiency.*—Kark and Lozner,[64] using a modified Quick test, reported on changes in the prothrombin time in patients with simple nutritional deficiency of vitamin K. Their four patients were free from jaundice and intestinal and hepatic disease but did have signs of other vitamin deficiencies. On vitamin K concentrate without bile salts the prothrombin time, after having been markedly prolonged in the diluted plasmas, returned to normal within three days in all cases. Although these patients had hemorrhagic manifestations, it was the opinion of these authors that they were due to deficiency of vitamin C. Scarborough,[65] using Quick's test as a measure of plasma prothrombin, was unable to corroborate the finding of Kark and Lozner in patients with multiple vitamin deficiency. He concluded that the explanation of their different results lay in the different technique of determining plasma prothrombin. In spite of an adequate intake of vitamin K and a normal output of bile, certain patients with poor intestinal absorption such as may be seen in sprue, ulcerative colitis, etc., may have lowered levels of plasma prothrombin and in a few instances develop the hemorrhagic tendency. Clark and his co-workers,[66] in 1939, reported their experience with a wide variety of gastrointestinal diseases and associated hypoprothrombinemia. Stewart and Rourke[27] observed patients with chronic ulcerative colitis who had diminished levels of plasma prothrombin which responded to oral vitamin K therapy. Mackie[67] found low levels of plasma prothrombin in a wide variety of conditions not associated with jaundice or obvious hepatic disease. He reported in detail the findings in two cases of regional enteritis and two of ulcerative colitis, one case of Banti's syndrome and one case of tropical sprue complicated by chronic intestinal obstruction. In three of these cases there was severe hemorrhage and in all of them the plasma prothrombin time was prolonged.

We[62] have followed quite by accident the plasma prothrombin in an interesting case of poor intestinal absorption of vitamin K in the absence of any clinical disease. The plasma prothrombin was determined at first as a control, and when the level of 52 per cent was found and repetition revealed this figure to be correct, careful studies were carried out to determine, if possible, the nature of the defect. Oral administra-

tions of 2 mg. of menadione produced no change in the level of the plasma prothrombin and similar failure of response followed menadione and bile salts in combination. However, intramuscular injection of 2 mg. of menadione produced a prompt elevation of the prothrombin which was maintained for one month. This patient has noted all her life an unusual tendency to bleed after minor trauma, dental operations, and tonsillectomy. Her diet has always been adequate in all respects. It would seem in this instance that we must postulate some defect of the intestinal absorptive mechanism.

E. *Hemorrhagic Disease of Newborn.*—In 1937, Brinkhous, Smith, and Warner[68] reported on the plasma prothrombin of newborn infants from the time of birth to ten and one-half months and observed extremely low levels during the first few days of life. Values ranging between 14 and 44 per cent of the adult normal were obtained and the normal level was approached by the age of ten and one-half months. Hellman and Shettles[69] confirmed the above findings and added that the levels of plasma prothrombin of premature infants were approximately one-third that of full-term infants, i.e., less than 10 per cent of the values of their mothers' prothrombin. Javert and Moore, [70] who employed the two-stage test of Warner, Brinkhous, and Smith, further confirmed these findings. In a series of twenty consecutive bloods taken at birth simultaneously from the cord and from the mother, the average level of the cord blood was 23 per cent and that of the mother 77 per cent.

Workers who have used the Quick prothrombin time as a measure of plasma prothrombin have obtained a variety of results from cord bloods. Quick and Grossman[71] stated that the blood of infants three to seven days old was essentially the same as adults' blood. In a group of eight published cases the clotting time was within one-half second of the normal control in every instance. One month later Quick and Grossman[72] reported three cases of cord blood with prothrombin levels of 71, 67, and 67 per cent, whereas in ten cases involving infants between the ages of six hours and two and one-half days the prothrombin percentage ranged between 80 and 7 per cent. In one instance the prothrombin rose from 15.5 per cent at the end of three and one-half days to 75 per cent at the end of five and one-half days. On the other hand, Norris and Rush[73] using the Quick test found that the prothrombin of cord blood in a series of fifty-one babies was 85 per cent and 63 per cent, depending on whether the plasma was undiluted or diluted with saline solution. Simultaneous determinations of the prothrombin of the mother's blood by the same technique revealed percentages of 117 and 140 respectively. Further confirmation of diminished levels of plasma prothrombin in newborn infants was added by Kato and Poucher,[74] who found in a series of 173 newborn infants average clotting times of 45 seconds on the first day

of life, 38 seconds on the second day, and a slower fall to 28 seconds by the twentieth day. Normal adult controls had clotting times averaging 20 seconds.

Waddell, Guerry, Bray, and Kelley,[75] who were the first to report on the effect of vitamin K on the plasma prothrombin of the newborn infant showed that there is a rapid and significant response in the prothrombin following oral administration of vitamin K concentrate. Shettles, Delfs, and Hellman[76] not only fed infants the vitamin but also observed the effect on the prothrombin of vitamin K administered to the mother before and during labor. This latter method produced an average elevation of plasma prothrombin in the infants to three times the normal controls.

Waddell and Guerry,[77] Nygaard,[78] Rhoads[52] and others have recorded cases of hemorrhagic disease of the newborn with low levels of plasma prothrombin.

Recently Maumenee, Hellman, and Shettles[79] studied the retina of newborn babies and found that those with retinal hemorrhage showed lower levels of prothrombin than normal infants and that administration of vitamin K to mothers prior to the onset of labor almost entirely eliminated retinal hemorrhage in their infants.

There has been much speculation about the underlying physiology of the hypoprothrombinemia of the newborn, its further fall during the first few days of life, and its elevation from the eighth to tenth day. It is Quick's opinion that infants are born with a normal level of plasma prothrombin and develop a fall in this substance during the first forty-eight hours of life due to the fact that there is no reserve of prothrombin in the fetus and to the physiologic strain put on the infant during the first few days of life.

The recovery of the plasma prothrombin which Quick has found to occur abruptly in the second week of life he believes is due to bacterial synthesis of vitamin K in the intestinal tract of the infants with subsequent absorption and utilization by the liver for the elaboration of plasma prothrombin.

Tocantins[80] studied an infant with a complete septum between the first and second portions of the duodenum in whom the bile duct connected with the distal bowel, with the result that no food could get to the intestine although a normal amount of bile was present. Clinically the infant became jaundiced on the second day of life, vomited all food, passed meconium by rectum, and showed evidence of prolonged bleeding from a skin puncture. The plasma prothrombin was less than 1 per cent of normal. By the eleventh day of life the jaundice began to clear, bile was passed by rectum, and the plasma prothrombin rose to 113 per cent of normal. Tocantins concluded from the above case that bacterial activity in the intestine with subsequent formation of vitamin K was not

the underlying mechanism in the elaboration of the plasma prothrombin during the second week of life but rather that the true mechanism lay in the implied impairment of hepatic function of the newborn infant as evidenced by the analogous condition of "physiologic" icterus of the newborn.

A possible criticism of the above hypothesis may be found in the fact that the plasma prothrombin response to vitamin K in the newborn compares favorably with that of the adult in whom normal liver function is present. If impairment of liver function in the newborn is the underlying mechanism of the hypoprothrombinemia, there should be little or no response to vitamin K so long as such impairment exists.

Javert and Moore[70] postulated that since the circulation of the blood of the fetus from the placenta to the heart circumvents the liver via the ductus venosus by as much as 80 per cent of its volume, the plasma prothrombin of the blood in the peripheral circulation should be greatly reduced. Andrus and Lord[81] constructed an Eck fistula in four dogs and observed a slow but steady fall in the plasma prothrombin to an average of 59 per cent of normal in an average of forty-three days. On the other hand, in three dogs with a reverse Eck fistula the plasma prothrombin averaged 89 per cent of normal at the end of an average of fifty-one days. In an Eck fistula the blood flow from the portal vein is shunted through the inferior vena cava and does not reach the liver due to ligature on the portal vein on the hepatic side of the anastomosis between the portal vein and the inferior vena cava. In the reverse Eck fistula the inferior vena cava is ligated cephalad to the anastomosis of the portal vein and the inferior vena cava and hence all the blood from the hind legs and pelvis pass through the liver along the portal flow.

From a therapeutic point of view it would seem best to treat all mothers just prior to or during labor with menadione and to administer the vitamin to the newborn infants if the level of prothrombin is low or if the infant should need any surgical procedure. On the pediatric service of the New York Hospital three infants have been observed who, following an episode of diarrhea, developed hemorrhagic manifestations associated with low levels of plasma prothrombin.[82]

F. *Hyperthyroidism.*—For many years it has been pointed out that the liver is altered anatomically and functionally in the hyperthyroid patient. Weller,[83] Beaver and Pemberton,[84] and Shaffer[85] demonstrated that a wide variety of pathologic changes occur in the livers of patients with toxic goiter and that these range from widespread acute necrosis (usually central) to chronic patchy parenchymatous interlobular hepatitis. Functional impairment of the liver has also been noted, and Boyce and McFetridge,[86] Bartels and Perkin,[87] and Haines, Magath, and Power[37] have reported carefully studied series of patients, concluding that in general the higher the basal metabolic rate the poorer the

hepatic function as indicated by the hippuric acid excretion test, and that there is usually a significant depression in hepatic function after operation. Crile,[88] using the bromsulphalein excretion test, found that impairment of hepatic function in the postoperative course of relatively sick patients was most marked in elderly individuals with long-standing hyperthyroidism. It is his opinion that the delayed (third to seventh postoperative day) reaction of confusion, delirium, jaundice, and bronchopneumonia occasionally seen in elderly patients who have had severe hyperthyroidism is a possible terminal event due to hepatic insufficiency.

We[46] have studied a group of thirty-six cases of toxic diffuse and toxic nodular goiter and found that the level of plasma prothrombin shows little or no correlation with the preoperative basal metabolic rate, age or sex of the patient, or with the duration of the disease. On the other hand, it appeared that there was a marked fall in the plasma prothrombin during the immediate postoperative period, averaging 15 per cent but amounting to 40 per cent or more in some cases. The lowered levels were seen soon after operation and the normal level was attained only after one week had elapsed. The curves are quite similar to those obtained with chloroform anesthesia in patients as reported by Cullen, Ziffren, Gibson and Smith.[48] In one patient who developed clinical jaundice (icteric index, 50) following a first stage hemithyroidectomy, the plasma prothrombin fell from a preoperative level of 61 per cent to 43 per cent of normal on the first day and to 28 per cent on the third day after operation. Subsequent rise to 60 per cent of normal had occurred by the sixth day.

The above findings bring further important evidence to bear on the role of the liver in the patient with toxic goiter and it would seem highly advisable to use every means at hand to improve the patient's hepatic function during both the preoperative period of preparation and the immediate postoperative phase.

LIVER FUNCTION TESTS IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

A wide variety of tests of liver function have been employed in an attempt to differentiate extrahepatic from intrahepatic jaundice but only a few of them have withstood rigid clinical application. There follows a comparison of the findings of those which have yielded the most accurate results.

A. *Galactose Tolerance Test.*—The galactose tolerance test was utilized by Shay and Schloss[89] and Schiff and Senior[90] with excellent results, being almost uniformly successful in the differentiation of the two groups of jaundice. On the contrary, Banks, Sprague, and Snell[91] found that the test was of no real value when used as a differential diagnostic aid. Recently Bassett, Althausen, and Coltrin[92] have brought forth a modification in the form of a galactose clearance test which appears to

provide a high degree of accuracy. They found that 82 per cent of a group of patients with obstructive jaundice of less than six months' duration had galactose clearance levels of less than 20 mg. per cent, while 81 per cent of the cases with idiopathic parenchymatous jaundice had more than 20 mg. per cent of galactose remaining in the blood seventy-five minutes after injection of 1 c.c. of a 50 per cent solution per kilogram. It would seem, however, that this overlap, although statistically small, may cause some limitation in the interpretation of the test in any given case of jaundice which presents a diagnostic problem.

B. *Cephalin-Cholesterol Flocculation Test.*—The other test to receive high recommendation in the differential diagnosis of jaundice is the cephalin-cholesterol flocculation test of Hanger.[93] In the hands of the author this test obtained an accuracy of 92 per cent, being correct in 58 out of 63 cases. Rosenberg[94] confirmed the findings of Hanger and made the observation that early in the course of jaundice a strongly positive flocculation test was indicative of an intrahepatic origin (8 out of 8 cases), whereas a negative or faintly positive test was suggestive of an extrahepatic cause for the jaundice. In 1 case out of 11 with obstructive jaundice a strongly positive test was obtained. On the other hand, Pohle and Stewart[95] found that the cephalin-cholesterol flocculation test is not satisfactory in the differential diagnosis of jaundice, although it is of marked sensitivity in the recognition of hepatic damage. In a series of twenty-three patients with obstructive jaundice, strongly positive (3+ and 4+) reactions were obtained in six instances. The duration of the jaundice in these six cases varied from two weeks to fourteen months, and the etiology of the obstruction included both malignant and benign causes for the extrahepatic block.

C. *The Level of Plasma Prothrombin and Its Response to Menadione.*—Lord and Andrus[62] have reported on the use of the response of the plasma prothrombin to intramuscular injection of menadione as a diagnostic aid in the differentiation of intrahepatic from extrahepatic jaundice. In a series of thirty-six cases of jaundice of intrahepatic origin the test was correct thirty-two times. In the group of extrahepatic jaundice it was correct in 49 cases out of 50. Hence, in a total of eighty-six cases where the test was applied, an accuracy of 94 per cent was attained. It is worth mentioning that there have been more than twenty cases of extrahepatic jaundice not included in the above group during the past year and a half in which the initial prothrombin was 80 per cent or more. We have found that every case of jaundice with an initial level of plasma prothrombin at 80 per cent or higher is one of extrahepatic origin. The technique of the test is to determine the level of plasma prothrombin on two successive days by the Warner, Brinkhous, and Smith test,[5] and if the two levels are within 5 per cent of each other, 2 mg. of menadione are injected intramuscularly and the prothrombin

is determined at intervals of twenty-four, forty-eight, and seventy-two hours. On the other hand, if there is a difference greater than 5 per cent in the two initial levels of prothrombin, the level is determined on the third day, and so on, until the levels on two successive days are found to be within 5 per cent of each other. When such agreement occurs, then the menadione is administered. On no occasion have we found it necessary to determine the prothrombin for more than three successive days before injecting menadione.

Simultaneously and independently Allen and Julian[31] reported on twelve cases of hepatic disease in which the response of the plasma prothrombin to the oral administration of menadione was sluggish or absent. They conclude, "that patients with chronic disease of the liver showed the most marked failure to respond to therapy. This, we believe, offers a characteristic of valuable diagnostic importance, in that failure of prothrombin response to adequate vitamin K in cases of jaundice would imply intrahepatic disease rather than obstruction of the bile ducts as the cause of the jaundice." Examination of their chart of twelve cases shows one patient with acute hepatitis and marked icterus who had an initial plasma prothrombin level of 41 per cent of normal, but which rose to 68 per cent after three days of treatment and to 95 per cent on the seventh day. This response, although not quite as rapid as is the typical case of extrahepatic jaundice, is at variance with our experience in which no case with catarrhal jaundice or acute hepatitis rose more than 29 per cent, and in the one case that rose by this amount a second trial of the test some two weeks later showed a fall of 9 per cent.

Recently, Olwin[63] confirmed the results of Lord and Andrus, and of Allen and Julian, except for the fact that he obtained a good response in the group of patients with catarrhal jaundice, and a failure to respond only in those patients with subacute yellow atrophy of the liver. Olwin and Lord and Andrus used the Warner, Brinkhous, and Smith test, while Allen and co-workers used their modification of the Quick test.[11]

THERAPY OF PROTHROMBIN DEFICIENCY

From the above discussion of the metabolism of vitamin K, its relation to the intestinal absorptive mechanism and the role of the liver in the elaboration of plasma prothrombin, it becomes clear that there are several factors in the treatment of hypoprothrombinemia. At present prothrombin as such can be administered only in the form of blood transfusion as no concentrate of this substance has been described for clinical use. However, a transfusion is only a temporary therapeutic measure. The administration of vitamin K is a vital factor and this can be given in a variety of forms and by several different routes. Finally, and perhaps of greatest importance in the therapy of hypo-

prothrombinemia, is the maintenance of adequate liver function as no amount of vitamin K will elevate the plasma prothrombin in the presence of a severely damaged liver.

A. *Blood Transfusion.*—Judd, Snell, and Hoerner[96] pointed out the value of a transfusion of blood in the hemorrhagic state associated with obstructive jaundice and though of transient effect, found that a transfusion a few hours before operation might prevent serious hemorrhage subsequently. Experimental evidence demonstrating the effect of blood transfusion in the hemorrhagic state was presented by Smith, Warner, Brinkhous, and Seegers.[57] They showed that the plasma prothrombin was elevated and hemorrhage controlled when a transfusion of blood was carried out in a dog with a cholecystnephrostomy and a markedly depressed level of plasma prothrombin. The improvement was of temporary duration and hemorrhage recurred in a few days.

From a clinical study Stewart[97] suggested that a 600 c.c. transfusion of blood elevated the plasma prothrombin approximately 6 per cent. In controlled experiments in the dog Lord, Andrus, and Moore[98] demonstrated that the change in the total content of prothrombin in the plasma of a recipient after a transfusion was dependent on the prothrombin content of the plasma of the donor and may be calculated on the basis of addition.

There has been much controversy on the question of efficacy of "bank blood" as a source of plasma prothrombin ever since the original paper by Rhoads and Panzer[99] who found that the prothrombin level of bank blood by Quick's method rapidly declined to less than 25 per cent of normal during the first seven days of storage. Lord and Pastore[100] were the first to report on the levels of plasma prothrombin in bank blood as measured by the Warner, Brinkhous, and Smith test and found that rather than declining rapidly as observed by Rhoads and Panzer, the plasma prothrombin remained above 80 per cent of normal during the first week of storage and fell to 61 per cent by the end of the third week. Using the Quick test on the same samples of blood, Lord and Pastore confirmed the findings of Rhoads and Panzer. Subsequently, Warner, DeGowin, and Seegers[101] confirmed the findings of Lord and Pastore when the Warner, Brinkhous, and Smith test was used, but did not observe a significant fall with the Quick test. However, Ziegler, Osterberg, and Hovig,[102] employing both tests, observed a slow, gradual fall in plasma prothrombin with each test (an average of 75 per cent in four days, 65 per cent in eight days, and 40 per cent in thirty-seven days), and Quick, using his own test confirmed the findings of Rhoads and Panzer, and Lord and Pastore when the Quick test was used. Numerous other reports have been made but there is complete agreement in only one fact, namely, that the plasma prothrombin remains above 70 per cent of normal during the first five to seven days of

storage when determined by the Warner, Brinkhous, and Smith test, indicating that bank blood less than one week old is an adequate source of plasma prothrombin.

B. *Vitamin K.*—Originally, crude concentrates of alfalfa, fish meal, and spinach were employed as the source of vitamin K. With these several authors reported on the successful control of the hemorrhagic diathesis associated with jaundice and biliary fistula and of hemorrhagic disease of the newborn.[25-27, 51, 68]

With the discovery that 2-methyl-1, 4-naphthoquinone and its derivatives were highly active antihemorrhagic substances and that they could be administered not only orally but also intramuscularly and intravenously, the therapy of hypoprothrombinemia was vastly improved. In addition, the role of the liver and of the intestinal absorptive mechanism became more clearly understood.

Intravenous administration of phthiocol by Butt, Snell, and Osterberg[104] and Smith, Ziffren, Owen, and Hoffman[50] was described in 1939 and both groups of workers observed excellent responses in the plasma prothrombin to this synthetic substance. Synthetic vitamin K_1 was used intravenously by Frank, Hurwitz, and Seligman[105] with prompt and prolonged effect in two patients with hypoprothrombinemia. MacFie, Bacharach, and Chance[106] were the first to describe the intramuscular injection of 2-methyl-1, 4-naphthoquinone, and with the use of 10 mg. doses observed significant elevation of the plasma prothrombin. Andrus and Lord[32] shortly thereafter confirmed the value of the intramuscular injection of 2-methyl-1, 4-naphthoquinone, obtaining excellent responses to 2 mg. doses in the absence of severe liver damage.

Rhoads and Fliegelman[107] reported the effectiveness of the oral administration of 2-methyl-1, 4-naphthoquinone in a group of ten patients. Shettles, Delfs, and Hellman[76] fed 2-methyl-1, 4 naphthoquinone to mothers in labor and to infants, and found it effective in elevating the plasma prothrombin.

The intravenous use of administration of other derivatives of naphthoquinone has been stressed by Olwin[63] as an ideal means of controlling hypoprothrombinemia. Both Olwin and Lord and Andrus have found parenteral routes for the administration of the synthetic vitamin K best for the differential diagnosis of jaundice.

Whether menadione is administered intravenously or intramuscularly, the effect on elevation of the plasma prothrombin is prompt (in 2 to 8 hours), significant (15 to 60 per cent rise in the absence of liver damage), and prolonged (7 to 20 days). Since in the parenteral use of vitamin K, bile salts are not necessary and the state of the intestinal absorptive mechanism and the presence of vomiting are of no consequence, there would seem to be little choice in the mode and route of

administration. Menadione should be used intramuscularly or intravenously in 2 mg. amounts every three to ten days, depending on the level of the plasma prothrombin. If there is no available means for determining the level of plasma prothrombin, then the injections should be carried out every three to four days until the basic condition (obstructive jaundice, biliary fistula, etc.) is rectified.

C. *The Protection of the Liver.*—During the past twenty-eight years factors which protect the liver from injury have been worked out on the experimental animal and subsequently applied to human needs. Thus, Opie and Alford[108] demonstrated the value of high carbohydrate diet in the protection of the liver of the rat against chloroform intoxication and also emphasized the ill effects of fat in the diet. This work has been repeatedly confirmed, but recently Johnson and his co-workers[109] observed that the proportion of fat in the liver was of more significance in the susceptibility of the liver to injury than the amount of glycogen present. It had been demonstrated earlier[110] that a high fat diet was harmful to the liver of the dog when carbon tetrachloride was used as the hepatotoxin, animals on a high fat diet living only three weeks, in contrast to similar animals which on a high carbohydrate diet lived three to four months.

There has been little or no dispute over the fact that a diet high in carbohydrate and low in fat was best for the damaged liver, but there has been considerable controversy over the relation of protein in the diet. Bollman and Mann[110] claimed that a diet of meat protein was harmful to dogs fed carbon tetrachloride and that in some of these dogs the survival period was considerably shorter than in the group fed a high carbohydrate diet. They felt that it was not the protein per se, but rather some water soluble substances of meat which were harmful, and hence that milk was a perfectly safe and adequate source of protein. Lord, Andrus, and Moore[44] confirmed the efficacy of a diet high in carbohydrate, low in fat, with milk as the source of protein in dogs with obstructive jaundice, demonstrating that animals on this carefully controlled diet lived on the average of seventy-five days, in contrast to a group of dogs which lived forty-seven days (an average) when kept on the regular balanced laboratory diet.

Recently, however, Messinger and Hawkins,[111] employing intravenous arsphenamine as the hepatotoxin found that a high protein diet (meat in the form of hamburg) protected the liver more effectively than any other diet. To quote from their paper: "in our experiments, the dogs with severe liver injury showed marked improvement when the diet was changed to protein, and there was not the slightest evidence that the meat diet was in any way injurious."

Johnson and his co-workers[109] demonstrated in dogs with the common bile duct ligated that a diet high in protein and carbohydrate with no fat

was more effective than the usual high carbohydrate diet in reducing the fatty acid concentration of the liver and in increasing the hepatic glycogen. This they have also confirmed in patients.

During the past three years experimental necrosis and cirrhosis of the liver have been produced in the rat[112] and rabbit[113] using special diets which were deficient chiefly in the B complex. Rich and Hamilton[113] found that rabbits fed a diet adequate in every respect except for the B complex developed cirrhosis of the liver in from 25 to 113 days. If all of the known synthetic vitamins of the B complex were added (thiamine, nicotinic acid, riboflavin, and B_6), the cirrhosis still occurred. However, if whole brewer's yeast was administered, the changes in the liver were prevented. Daft, Sebrell, and Lillie[114] were able to produce cirrhosis of the liver in rats on a special diet and could prevent it by adding casein (30 per cent of the diet), methionine (0.7 per cent of the diet), or choline (20 mg. daily) either singly or in combination.

Drill and Hays,[115] from a different viewpoint, demonstrated the value of whole brewer's yeast in maintaining normal liver function in the dog, as measured by the bromsulphalein test, when thyroid extract was administered.

Andrus and Lord[116] have found that a minute amount of chloroform (0.12 c.c. per kilogram) when injected subcutaneously in the dog regularly produces a fall in the plasma prothrombin to 50 per cent of normal in twenty-four hours and that this fall is not recovered from until one week has elapsed. The range of fall of the plasma prothrombin varies in individual dogs from 73 to 2 per cent of normal, but the mean average is approximately 50 per cent. However, when whole brewer's yeast is administered in 1 Gm. per kilogram doses for from two to three days preceding the administration of the hepatotoxin, the fall of plasma prothrombin is cut in half and the period of recovery shortened to from four to five days.

Studies of some of the individual factors in the B complex reveal that thiamin, riboflavin, and nicotinic acid have no effect whatsoever in preventing the fall of plasma prothrombin after the test dose of chloroform. On the other hand, choline chloride in 200 mg. per kilogram doses for three days prevented the fall in the plasma prothrombin to a degree equal that of brewer's yeast. Because of the remarkable effect of brewer's yeast and of choline in protecting the liver from the action of chloroform, it would seem wise to include these substances in the diet of all patients with potential or actual damage to the liver.

The effect of anoxemia in producing hepatic damage has been demonstrated[117] and should be borne in mind in selecting the anesthetic agent in patients with diminished liver function. Anemia, because of the anoxic effect it may have on the cells of the liver, should be corrected.

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Review of Recent Meetings

SECTION ON SURGERY, GENERAL AND ABDOMINAL, OF THE AMERICAN MEDICAL ASSOCIATION MEETING AT ATLANTIC CITY, N. J., JUNE 8-12, 1942

J. D. Martin, Jr., M.D., Atlanta, Ga.

THE following papers were presented at the American Medical Association Meeting at Atlantic City, June 8-12, 1942, section on general and abdominal surgery.

Edgar J. Poth, Baltimore: reviewed the experience in the use of succinyl sulfathiazole in the care of patients subjected to large bowel operations. The altered intestinal flora permitted extensive surgical procedures with little danger of local infection or peritonitis, as was shown by a representative series of cases. It was noted that there was a reduction in the incidence of the ordinary camplications.

Frank Lahey, Boston: **Lesions of the Right Colon Involving Colectomy.**—The diagnostic features were presented in 127 resections for lesions involving the right colon. Very advanced cases of secondary anemia can be present in cancer of the rectum and still be operable, while similiar lesions in the left colon would indicate inoperability. Lesions involving the terminal ileum of regional ileitis which extend over onto the right colon were presented. The relationship of the infected glands in the entire right mesentery to recurrence of regional ileitis were presented. It was advocated that the right colon, hepatic flexure, and right half of the transverse colon should be removed, in order to remove suspicious mesentery in regional ileitis. In acute stages of regional ileitis, operations should not be performed. The mortality in this series of cases was 11.7 per cent. In the right side of the colon, 53.6 per cent were living at the end of five years.

Harvey B. Stone and **Samuel McLanahan,** Baltimore: **Resection and Immediate Anastomosis for Carcinoma of the Colon.**—The method of treatment was presented for resection and immediate anastomosis by the aseptic technique, in which the results obtained were comparable to those achieved by other methods. Statistics were shown in their personal cases, that in the majority of cases such a method could be safely employed. Preliminary or simultaneous decompression of the intestine had been occasionally employed.

Thomas E. Jones, Cleveland: **Complications of Combined Abdomino-perineal Operations Presented in 500 Cases.**—The most common complication was referable to the bladder, and is probably due to destruction of the sympathetic nerves necessitated by this radical procedure. Infection was shown to cause considerable annoyance. Pulmonary complications were reported to be rare. Wound infections, which formerly occurred in 25 per cent of the cases, had been reduced in the past five years to approximately 2 per cent. Femoral phlebitis and hemorrhage were rare. Prophylactic and therapeutic effort was advocated in the prevention of these complications.

Charles B. Puestow, Chicago: **Experimental and Clinical Studies of Intestinal Motility and Postoperative Distention.**—It was noted in experimental evidence that there was a contrary action of the large and small bowels. That is, when one is motile, the other is quiet, and vice versa. Drugs which stimulate small bowel motility, as opiates, prostigmine, physostigmine, and acetylcholine derivatives, inhibit the colon. Drugs which stimulate the colon, as solution of posterior pituitary and pitressin, inhibit the small bowel. The importance of these factors was stressed in the production of gas pains and postoperative distention.

I. S. Ravdin, Philadelphia: **The Prevention of Liver Damage and the Facilitation of Repair in the Liver by Diet.**—It was shown that glycogen does not directly protect the liver from injury, and its effect is completely indirect. An adequate amount of proteins in the diet will protect the liver from injury. This action is brought about by the lipotropic action and some direct protection by certain components of the protein molecule. Experimental evidence, both in animals and man, showed what was accomplished by intravenous administration of dextrose and diet. This data was in agreement in that it is not possible greatly to influence the composition of the liver solely by intravenous therapy. A sufficient amount of adequate foodstuffs are necessary to meet the energy requirements of the patient and to provide for deposition in the liver.

J. Ross Veal, Washington, D. C.: **Prevention of Pulmonary Complications Following Thigh Amputations by High Ligation of the Femoral Vein.**—Pulmonary complications following thigh amputations were reported as being the chief factor in the high morality rate. The author advises preliminary high ligation of the femoral vein before amputation to close the source of emboli. In 114 thigh amputations without ligation of the femoral vein, there were 69 deaths, 42.2 per cent of them resulting from pulmonary complications. In 80 thigh amputations in a similar group of vascular gangrene cases in which a preliminary high ligation of the femoral vein was performed, there were 14 deaths. There was only one pulmonary complication. The technique of high ligation of the femoral vein was reported.

W. J. Potts, Oak Park, Illinois: **Pulmonary Embolism.**—In experimental work done on dogs, the external jugular and femoral veins were partially occluded with a single silk ligature. No thrombosis followed. In a second group of experiments, the veins were doubly partially occluded with silk ligatures placed 1 to 2 cm. apart. In the external jugular veins, thrombosis developed in one of fourteen experiments. In the femoral vein, thrombosis occurred in twelve of twenty-two experiments. It appeared that an alteration in the rate of venous blood flow was a factor in the formation of thrombi.

Arthur W. Allen, Boston: **Subtotal Gastrectomy for Stenosing Duodenal Ulcer, (Chairman's Address).**—A review of this subject was presented with an analysis of the various factors involved in cure from methods other than subtotal resection of the stomach. It was shown that the results obtained from subtotal gastrectomy were by far more beneficial than by other methods. A motion picture was shown demonstrating the author's method of performing a subtotal gastrectomy. In this procedure, resection is performed from the fundus end and the removal of the pyloric end is done after mobilization of the stomach and first portion of the duodenum.

Harry E. Mock and **Harry E. Mock, Jr.,** Chicago: **Management of Skull Fractures and Brain Injuries.**—A study of 6,462 cases of consecutive proved skull fractures was presented for the purpose of evaluating the best types of management of

brain injuries. These were collected from representative hospitals in every part of the country. The mortality rates varied from 17 to 49 per cent. Over 50 per cent of the hospitals had a mortality rate above 33 per cent. The immediate management of cerebral shock, overcoming anoxemia and ischemia of the injured brain by use of oxygen, adequate dehydration, and spinal drainage, avoiding oversedation, operating when indicated but not too early, and the diagnosis of associated injuries was advised in an effort to reduce the mortality rates.

J. D. Martin, Jr. and **Robert Mabon**, Atlanta: **Pulsating Exophthalmos.**—The pathologic aspects of this condition were shown to be well established in the traumatic type, to be a communication between the internal carotid artery or its branches, and the cavernous sinus. Anatomic dissections were presented which established the relationship of these structures, and explained the possibility for the development, both in the traumatic and spontaneous lesions. A review of the literature with the results obtained by the various methods of treatment was presented. It was shown that in ligation of the internal or common carotid artery, the results were essentially the same. A report was made of five cases which were treated by proximal ligation. Two cases were spontaneous in origin; three were traumatic.

George M. Curtis and **James D. King**, Columbus, Ohio: **Blast Injuries to the Lungs.**—The pressure wave of the blast from a bomb explosion was shown to produce serious pulmonary injuries without resultant evidence of injury to the thoracic cage. The lesions are principally due to the impact on the body wall of the pressure component of the blast wave. Lung injury without external evidence of trauma occurs more frequently in peace time than has been previously recognized and reported. The mechanism responsible for the cerebral lesion is the hydraulic pressure on the firmly encased central nervous system, resulting from sudden compression of the thoracic cage with consequent violent back pressure on the venous side. After injury, complete rest is essential; every effort should be made to avoid any additional trauma.

Harold L. Foss, Danville, Pa.: **Total Hysterectomy.**—A total hysterectomy was said to be the operation of choice in malignant processes involving the fundus of the uterus. A simplification of this procedure has been advised. A facilitation of this has been done by the use of a long-handled knife and a right-angle clamp. The mortality rate of total hysterectomy can be lowered by such a procedure.

U. V. Portmann, Cleveland: **Classification of Primary Cases of Cancer of the Breast.**—The most important factor governing prognosis and indications for different therapy is thought to be the extent of involvement. This can be determined by recognition of clinical and pathologic manifestations. A classification for primary cases of cancer of the breast was presented on clinical and pathologic information.

Frank E. Adair, New York: **The Role of Surgery and Radiation in Cancer of the Breast.**—A study of 7,215 cases of cancer of the breast treated at the Memorial Hospital in New York was presented. An evaluation of various methods of treatment, including x-ray, radium, and surgery, was made. The results obtained from these various methods has brought about a tendency among many surgeons to consider simple mastectomy followed by roentgen therapy in lieu of the radical amputation.

Robert Elman, St. Louis: **Acute Protein Deficiency in Shock, Burns, Intestinal Obstruction and Peritonitis.**—These conditions have in common a serious deficiency in the protein content of the plasma. Acute hypoproteinemia is usually, but not

always, easy to detect because it is often masked by dehydration. Replacement therapy is effective largely with rapid correction of protein deficiency. Plasma transfusions produce such a change, although large volumes are sometimes necessary. Saline and dextrose solutions alone are ineffective and often do harm. The intravenous injection of proteins is a newer way of correcting acute protein deficiency and holds great promise of success.

Elliott C. Cutler and **Robert Zollinger,** Boston: **Acute Cholecystitis.**—The authors presented three types of acute cholecystitis: (1) Patients in whom signs and symptoms subsided rapidly when treated with rest, removal of pain, and administration of adequate fluids; (2) patients who continue to show increasingly acute signs in spite of general supportive methods; and (3) patients, who in spite of rest and establishment of fluid and chemical balance, change little. It is felt that operation in this group should be performed after thirty-six to forty-eight hours of observation, after one is certain that the patient is not improving.

F. W. Gaarde, L. E. Prickman, and **J. H. Raszkowski,** Rochester, Minn.: **Is the Asthmatic Patient a Good Surgical Risk?**—The most important factor in reduction of mortality rate in asthmatic patients depends on careful selection of patients, observance of preoperative and postoperative precautions, and close cooperation between the medical and surgical staffs caring for these patients. A study of 189 consecutive cases of asthma to have major surgery at the Mayo Clinic disclosed that some form of postoperative pulmonary complication, including severe asthma, developed in twenty-five, or 13 per cent of the cases. Four, or 2.1 per cent of the patients died. Operative procedure on the upper part of the abdomen, which resulted in a lowering of the vital capacity, carries a special hazard for patients with asthma.

Wm. Bates, Philadelphia: **Intraspinal Administration of Ammonium Sulfate.**—The use of ammonium sulfate intraspinally was presented as a new form of therapy to aid in the control of intractable pain. Clinical application of the pitcher plant, **Sarracenia purpurea,** was carried out over a period of ten years. Identification of the ammonium as the active component of the pitcher plant and the action of the ammonium ion on the nerve impulses was demonstrated, showing the optimal concentration of the ammonium salts. The absence of action on the motor nerves was shown in optimal concentration. Selection of patients was reported in which intractable pain was relieved with ammonium salts intraspinally.

THE TWENTY-FIFTH ANNUAL MEETING OF THE AMERICAN BRONCHOESOPHAGOLOGICAL ASSOCIATION

PAUL HOLINGER, M.D., CHICAGO, ILL.

THE twenty-fifth annual meeting of the American Broncho-Esophagological Association was held July 8 and 9, 1942, at the Hotel Dennis, Atlantic City, N. J.

W. Likely Simpson, Memphis, Tennessee, presided. In his presidential address, Simpson discussed the technical, medical, and organizational problems in bronchoesophagology at the University of Tennessee School of Medicine. Endoscopic work is divided between the departments of otolaryngology and thoracic surgery. The staff of the former is composed of rotating interns, full-time residents, and six attending otolaryngologists who divide the service throughout the year. Clinical material is drawn from cases regularly assigned to the department and from consultations with

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other departments with the exception of the department of chest surgery, which makes its own bronchoscopic examinations. From a clinical standpoint, cases of nonspecific esophagitis associated with anemia are found to be of particular interest. Simpson reviewed this subject and added that the clinical picture is still as puzzling as it was twenty-five years ago.

F. W. Davison, Danville, Pa., presented a case report of a male, aged 70 years, who for three years had had a sensation of fullness in his throat but had no real dysphagia. When gagged, he regurgitated a long, pink, smooth mass of tissue one inch in diameter, which hung down two inches below his chin. Direct laryngoscopy showed that the pedicle was attached to the left lateral wall of the laryngopharynx. It was ligated and excised with the cutting current. It measured eight inches in length and one inch in maximum diameter, and histologic section showed it to be a fibrolipoma.

Emil Lois Van Loon and **Sidney Diamond** (by invitation), Philadelphia: **Foreign Bodies in the Gastrointestinal Tract.**—They discussed the problem of management of foreign bodies which had reached the stomach or intestines, as illustrated by analysis of the records of 386 consecutive cases of radiopaque foreign bodies in the stomach or intestines seen in the Chevalier Jackson Bronchoscopic Clinic at Temple University Hospital. Thirty-eight per cent were in the stomach and 62 per cent in the intestine when first seen. Of the more common foreign bodies, 49 were straight pins, 40 coins, 40 open safety pins, 29 closed safety pins, 29 bobby pins and 26 nails. Most of the patients were small children. Nineteen (48 per cent) of the forty with open safety pins were infants less than one year of age. There was no mortality in this group of 386 patients. In 17 patients in whom the foreign body did not pass beyond the pyloris, it was removed by fluoroscopically guided open-tube gastroscopy in 14 and by external operation in 3. Duodenotomy was done in 4 cases. Penetration of the gastric or duodenal wall by the point of the foreign body led to laparotomy in 5 cases. In only one of these cases had perforation been accompanied by symptoms of the perforation, but the diagnosis had been established roentgenologically in each instance.

L. Chester McHenry, Oklahoma City: **Two Cases of Mediastinitis Following Esophageal Foreign Bodies.**—Two patients were presented, each of whom had had evidence of cervical mediastinitis upon admission, following attempted swallowing of bones. External surgical drainage was necessary in each case, and, although a very stormy clinical course ensued, both eventually completely recovered. In neither instance was the foreign body recovered. The author stressed the importance of chemotherapy in the management of these patients.

Sydney S. Gellis (by invitation) and **L. Emmett Holt, Jr.** (by invitation), Baltimore: **The Prophylaxis of Lye Strictures of the Esophagus.**—Gellis and Holt describe the technique and results of the Salzer method of the treatment of lye burns of the esophagus as routinely employed at the Harriet Lane Home. Immediate attempts are made to neutralize the corrosive with weak acid, and visible burns are treated locally. Dilatations are started with bougies in the form of soft rubber catheters, 14 to 30 French, tapered and closed, filled with small lead shot. Dilatations are done daily and are begun at once unless there is great swelling of the fauces, when they may be postponed no more than three or four days. The child is held in a sitting posture during dilatation. Dilatations are done daily for two weeks, three times a week for two weeks, twice a week for two months, once a month for six months, and two or three times a year for several years. Of 41 children adequately treated according to Salzer's method, only one developed a stricture. Of 14 who received no treatment, 6 developed strictures. Not a single accident and

no deaths occurred in the group. Of 39 children who had fully developed strictures when first seen, 4 died following esophagoscopy, one of an esophagotracheal fistula, one of peritonitis following gastrostomy, one suddenly following gastrostomy, and one of pneumonia.

Samuel Iglauer, Cincinnati: **A Case of Myoblastoma of the Larynx.**—Iglauer presented a case of this type of tumor of the larynx and summarized the eight cases previously reported in the literature. The neoplasm was a pedunculated tumor with its pedicle between the arytenoid cartilages. The exact diagnosis was made only after the tumor had been removed and examined microscopically.

Fletcher D. Woodward and **William W. Waddell, Jr.** (by invitation), Charlottesville, Va.: **Bronchoscopy in the Newborn.**—The indication for bronchoscopy in the newborn exists after the usual procedures have failed to either clear the lung or establish a diagnosis. By a series of case reports the authors demonstrate that the procedure may be done with safety and benefit to the patient and, consequently, should be used more frequently. Aspiration of secretions in eleven of seventeen newborn infants, two of them premature, resulted in immediate relief of symptoms. In the remainder of the cases the procedure aided in establishing the diagnosis. In one of the infants, a four-pound premature one, the diagnosis of congenital absence of the left bronchus and left lung was corroborated by a lipiodal instillation of 2 c.c. of the oil through the larynx, the oil subsequently being aspirated bronchoscopically.

Kenneth A. Phelps, Minneapolis: **Some Further Observations on Tuberculous Tracheobronchitis.**—Phelps presents his opinions regarding tracheobronchial tuberculosis based on over 200 examinations made at Glen Lake Sanatorium in addition to those presented in previously published works. He stresses the fact that the ultimate prognosis in each case is dependent upon the general tuberculosis outlook of the patient and not upon the local disease of the bronchus. He does not believe that collapse therapy is responsible for the tuberculous bronchitis, but rather that it is a failure of successful pulmonary collapse and a cause of chronicity in pulmonary tuberculosis. In his series the lesion occurred almost exclusively in women, 63 to 2. The sanatorium population was 52 per cent men and 48 per cent women. The most reliable clinical signs of bronchial tuberculosis were found to be those due to an obstruction of the bronchus, namely, a wheeze or retention symptoms, and a positive sputum. Roentgenologically, obstructive emphysema, atelectasis, tennis-ball cavities, bronchograms, and laminograms gave evidence of bronchial tuberculosis. Bronchiectasis was proved to exist in 80 per cent of the cases and was suspected in 16 per cent more. Regarding therapy, Phelps states guardedly that local application of 30 per cent silver nitrate helps many patients. Some become sputum-free, at least for a while, some breathe better and apparently heal more quickly. In his experience, local treatment of the fibrotic stenoses by dilatation is not satisfactory. End results of his series are 31 per cent dead in five years, 63 per cent have chronic disease, and 6 per cent are well.

Edward A. Looper, Baltimore: **Bronchoscopic Involvement in Purpura Hemorrhagica.**—Looper described the case of a male patient, 31 years of age, who gave a history of repeated attacks of hemoptysis during the past seven months. Tuberculosis, malignancy, and bronchiectasis had been suspected but were not confirmed by the bronchoscopic findings. Numerous blood clots and mucus but no ulcerations of the mucous membrane were seen. The patient died some months later, and the post-mortem examination revealed the diagnosis to be purpura hemorrhagica. This case was presented to place it on record as one of the causes of undiagnosed cases of severe pulmonary hemorrhage.

Robert E. Parrish, San Antonio, Texas: **Respiratory Tract Hemorrhage a Bronchoscopic Problem.**—The author presented a general consideration of hemorrhage from the respiratory tract, placing special emphasis on diagnosis by means of bronchoscopic examination. In most instances the location and cause of the bleeding is revealed, but in some cases all present methods fail to reveal the etiologic factor, the hemoptysis remaining unexplained even on post-mortem examination in a few instances.

Robert L. Moorhead, Brooklyn, N. Y.: **Foreign Body in Right Upper Lobe Bronchus for Two Years.**—A foreign body, a lather's nail, was found in the right upper lobe bronchus of a draftee referred for examination of the chest because of a chronic cough. Bronchoscopic attempts at removal were unsuccessful because of the angle of the nail in the upper lobe bronchus. To facilitate removal of the nail, an artificial pneumothorax was instituted, straightening the bronchus and allowing free extraction of the foreign body. Recovery was complete and uneventful.

In the discussion, **A. H. Andrews, Jr.,** Chicago, warned against the use of this method in cases of foreign bodies with the point downward and the head fixed in edematous bronchial mucosa due to the possibility of perforation of the lung by the point with a resultant empyema.

M. C. Myerson, New York City: **A Bronchoscopic Diagnostic Sign for Pleural Cavity Lesions.**—Myerson has noted varying degrees of passive congestion in circumscribed areas of the bronchial tree during bronchoscopic examinations of patients with lesions in the pleural cavity. This bronchoscopic finding is offered as a new diagnostic sign.

William A. Hudson, Detroit: **Carcinoma of the Esophagus; Some Observations With Two Case Reports.**—Hudson presented two cases of postcricoid carcinomas of the esophagus which were seen relatively early. In the first a laryngectomy was done and the tumor removed in its entirety. While still further plastic repair is contemplated, the patient is alive, well, and happy three years after the operation and has maintained her weight. In the second case, with a lesion similar to that of the first, the patient refused the extensive surgery recommended and has had a recurrence of her lesion in the larynx itself, the area the patient had refused to allow to be removed. Hudson stresses the importance of the removal of the entire larynx as well as the esophagus when the common partition is involved.

William A. Lell, Philadelphia, Pa.: **Bronchoscopy as an Aid in the Treatment of Allergic Pulmonary Disease.**—The author pointed out that bronchoscopic aspiration of patients in status asthmaticus is associated with remarkable relief. It aids diagnostically through direct inspection, ruling out lesions such as foreign bodies and tumors which may simulate status asthmaticus. An aid in treatment is the collection of uncontaminated bronchial secretions for bacteriologic study and preparation of an autogenous vaccine. The results of a large series of cases treated bronchoscopically were reviewed and pathologic changes in the lungs, as observed at autopsy in five cases, were presented.

At a combined meeting of the **American Broncho-Esophagological Association** and the **American College of Chest Physicians,** held Monday afternoon, June 8, under the chairmanship of W. Likely Simpson and J. Winthrop Peabody, presidents respectively of these two organizations, the following papers were presented.

Louis H. Clerf, and **C. J. Bucher** (by invitation), Philadelphia, Pa.: **Adenoma (Mixed Tumor of the Bronchus).**—Of a total of 278 cases of primary bronchial

neoplasms that these men have examined, 35, or 12 per cent, have been the benign glandular tumors of the bronchus now called adenomas. Originally these were classified as adenocarcinomas and endotheliomas. Of their 35 patients with adenomas, 43 per cent were less than 30 years of age, 54 per cent of them females. Hemorrhage was an early symptom in 46 per cent, atelectasis in 15 patients, obstructive emphysema in 4, and almost all had had one or more attacks of pneumonia. The tumor was found in the left lung in 21 patients, in the right in 14. The bronchoscopic findings in these cases consist of partial or complete obstruction of the bronchus by a smooth mass. Ulceration rarely is noted. However, the authors emphasize the fact that the bronchoscopic appearance of the lesion gives no evidence of what may be present outside of the bronchus. Tomography may aid in obtaining this information. Treatment depends on a number of factors. Bronchoscopic removal of the lesion is advised if this is possible, but surgical removal is indicated if there is evidence of extrabronchial extension of the tumor. Some of the cases reported have been under observation for as long as fifteen years, and one patient is alive and well twelve years after electrocoagulation of the tumor. Of the patients presented in this series, there have been four deaths which have resulted directly from the tumor. Two of these resulted from bronchiectasis, one from pneumonia which probably was dependent on bronchial obstruction and one from carcinoma which developed at the site of an adenoma of five years' duration. There were four deaths due to unrelated causes. One of these patients had been free from tumor for eleven years. Seven patients are well and free from symptoms although there still is evidence of tumor present. Four patients have tumor with symptoms present; three of these have definite bronchiectasis and a fourth has paroxysms of coughing with occasional infection distal to the tumor which is an extrabronchial producing compression stenosis. This patient undoubtedly has bronchiectasis distal to the stenosis. Two patients have bronchiectasis without symptoms and an absence of tumor. They have been tumor-free for seven and ten years respectively; seven are tumor-free for periods varying from five to eleven years and also are free of symptoms. One has adenoma in both main bronchi and presents a hopeless problem. Three recently have come under observation. Two of these should be treated surgically for in one the tumor in the right upper lobe bronchus is inaccessible to bronchoscopic treatment and the other has a large extrabronchial tumor in the lower lobe of the left lung which is producing compression stenosis. The third case is being treated bronchoscopically. Surgical treatment has been recommended in six cases because of inaccessibility of the tumor to bronchoscopic treatment, the presence of extrabronchial adenoma or the occurrence of chronic pulmonary complications which cannot be relieved because of bronchial obstruction. Three have been treated surgically by lobectomy and two by pneumonectomy. There was one operative fatality. This patient had an empyema and was a poor surgical risk.

In the discussion, **John Kernan,** New York, emphasized the early age of patients in whom the diagnosis of adenomas had been made. Three of his patients were 13, 14, and 17 years old, respectively, and one, a patient of 46 years of age, had had symptoms since 1910. He was of the opinion that all these patients should have surgical removal of the involved lobe or lobes, since he felt the tumors all recurred, or were complicated by bronchiectasis in the lung distal to the tumor. In closing the discussion, **C. J. Bucher,** Philadelphia, described the microscopic appearance of the lesion, dividing adenomas into three groups: First, those with well-formed alveoli, with few of the cells in mitoses; second, those with a less evident alveolar arrangement with large glands and large cells; third, those containing considerable fibrous tissue, with masses of cells in cylindrical form or in clusters. He stated the tumors are covered with bronchial epithelium but have no capsule. There was no correlation between the histologic classification and the clinical course of the disease in these patients.

Paul H. Holinger, Chicago, Illinois: **Kodachrome Visualization of the Physiology and Pathology of the Tracheobronchial Tree.**—Color motion pictures taken through the bronchoscope were used to demonstrate various physiologic phenomena which occur in the normal bronchial tree. The film presented showed the increase and decrease in the diameter of the bronchi as well as the lengthening and shortening which occurs with respiration. By means of foreign bodies introduced into the bronchi of anesthetized dogs, various obstructive phenomena were illustrated. The mechanism of a wheeze, of the check-valve and ball-valve obstruction, and of complete obstruction producing atelectasis were shown as they appear bronchoscopically. To illustrate these various phenomena in the human being, the trachea and bronchi of patients with obstructing lesions were photographed bronchoscopically. Bronchiectasis, asthma, pulmonary adenoma, and bronchogenic carcinoma having distinct bronchoscopic features served to demonstrate the physiologic and pathologic processes of the bronchi.

The camera devised for this endoscopic photography consists of a magazine-loading 16 mm. camera and an f2.7 three-inch lens. Illumination of the small endoscopic field is obtained by directing the image of the ribbon of a ribbon-filament projection lamp onto a forty-five-degree mirror which encroaches on the lumen of the endoscope. This type of axial illumination provides adequately the illumination essential to color photography. A specially constructed telescope inserted into this system permits visualization of the field being photographed not only during the finding but also during the actual filming.

Book Reviews

Roentgen Treatment of Injections. By James F. Kelly, M.D., and D. Arnold Dowell, M.D. Cloth. Pp. 432, with 122 illustrations. Chicago, 1942, The Year Book Publishers.

This readable book emanates enthusiasm for the use of roentgen therapy to a degree not supported by most physicians. There are several sections with which general agreement will be found, such as those dealing with treatment of suppurative parotitis and erysipelas, but in regard to gas bacillus infection, peritonitis following appendicitis, and pneumonia, the book is far less convincing. With regard to gas bacillus infection, inadequate controls are given, either in treatment of the developed disease or in prophylaxis. The figures to support the argument for the efficacy of roentgen therapy are drawn from diffierent eras and areas and from different types of accessory treatment and authors, from the so-called "control" observations. In the treatment of peritonitis following appendicitis, the figures are also unconvincing, for, although the mortality rates for peritonitis treated with supportive measures and roentgen radiation are very little higher than a recent report on results using conservative measures alone, the control group showed mortality rates so unusually high (65 per cent) that one is led to doubt the value of the comparison. In regard to the treatment of pneumonia, individual cases are presented without control data, and one is at a loss to decide for himself the value of the therapy.

Despite these objections, the volume is very readable, and it provides a reference book of details of treatment which should certainly be borne in mind in the further evaluation of roentgen therapy of infections.

The Management of Fractures, Dislocations, and Sprains. By John Albert Key and H. Earle Conwell. Ed. 3. 1303 pages, 1259 illustrations. St. Louis, 1942, C. V. Mosby Company.

All surgeons familiar with the previous editions of this eminently successful text, appearing in 1934 and 1937, will undoubtedly receive the third edition with eagerness and enthusiasm. The book is divided into two parts and arranged in a manner similar to that of the previous editions. However, many of the chapters have been completely revised and rewritten with the inclusion of more modern concepts of therapy and current and timely considerations of certain types of injuries. Thus, the chapter on Compound Fractures includes a new section on war injuries. Moreover, the therapeutic considerations in this chapter have been completely rewritten to conform with the current concepts based upon the use of the sulfonamides. Noteworthy changes have also been made in the chapters on fractures of the humerus, hip, foot, and on injuries of the spine, in which is included a section on lesions of the intervertebral disc and of the ligamentum flavum. In general, the book is an authoritative, comprehensive, and up-to-date consideration of the subject, and in view of the current conflict, in which such conditions assume greater significance, the book will be received with even more enthusiasm than the previous editions.

Surgical Physiology. By Joseph Nash, M.D. Ed. 1. Pp. 496. Springfield, Ill., 1942. Charles C Thomas. $6.00.

This book might well be called a textbook of physiology for surgeons. It deals with physiologic processes of special interest to the surgeon. The practical aspects of pathologic physiology are emphasized, yet rightfully the author expends greater time and space in interpreting normal physiologic processes. As far as this reviewer's experience goes, a text just like it, covering the broad field of physiologic processes in surgery, has never appeared previously. Rost's *Pathological Physiology of Surgical Diseases* had a distinctly more clinical and less physiologic viewpoint than that reflected in this book. It is evident that the author of this monograph has a valuable background of training in the teaching of physiology. Now that he has identified himself with clinical surgery, it is to be hoped that in successive editions he will be enabled to bridge even more usefully the rather broad gap still existing between the discovery of physiologic fact and its adoption in practice in the clinic.

This is a useful and important book. It can be recommended enthusiastically to surgeons. A careful perusal of it will help surgeons to a better understanding and interpretation of normal and disturbed physiologic processes and thereby make them better surgeons.

Diseases and Injuries of the Larynx. By Chevalier Jackson, and Chevalier L. Jackson. Cloth. Pp. 663, with 200 illustrations. Philadelphia, 1942, W. B. Saunders Company. $8.

When Jackson and Jackson, in 1937, published their first edition, it received a warm welcome and was readily acclaimed the best book on this subject in the English language.

The authors now have published their second edition which incorporates much of the first plus the added developments in the field of laryngology up to the present time.

Every phase of laryngology is discussed in that typical and thorough style which so characterizes the Jacksons. Therapy and surgery for all conditions pertaining to the larynx are discussed at length and the new King operation for bilateral recurrent paralysis is given due recognition.

Probably one of the most interesting chapters in this book is the one on war surgery of the larynx which discusses all laryngeal trauma of war as well as of industrial and accidental surgery. This particular chapter should be read by every laryngologist.

This work is an outstanding contribution to laryngology by men whose clinical experience and scientific research eminently qualify them to produce such a masterpiece.

Carcinoma and Other Malignant Lesions of the Stomach. By Waltman Walters, B.S., M.D., M.S., Howard K. Gray, B.S., M.D., M.S., and James T. Priestly, B.S., M.D., M.S., Mayo Clinic and Mayo Foundation, Rochester, Minn. Ed. 1. Pp. 576, with 141 illustrations. Philadelphia, 1942. W. B. Saunders Company.

This monograph summarizes the experience of the Mayo Clinic with the management of carcinoma of the stomach over a forty-year interval (1907 to 1938). During that period of time 6,242 patients with cancer of the stomach were submitted to operation. Resection was done in 2,772 or 44.4 per cent of the patients operated upon. The mortality of the resection group was 16.2 per cent, a remarkable achievement considering the years of treatment under discussion. This is an

accomplishment, for the period, which excels the best performance of American surgical clinics in dealing with cancer of the stomach, speaking eloquently for the high standard of the surgery established by the Mayo brothers. At the present time, it should be remarked that this record of accomplishment is being equaled and surpassed today in many surgical clinics in America, affording proof that surgery is being improved, not alone by progress within the specialty itself, but also through new discoveries in related fields.

Perhaps the most valuable portions of this monograph are the detailed tables in the last section of the book, detailing the various factors which bear on operability, mortality, and prognosis. Whereas only 6.2 per cent of patients observed to have carcinoma of the stomach survived five years, the writers found that 28.6 per cent of the resection group survived for five years; at ten years, 20.3 per cent were still alive; at fifteen years, 15.5 per cent, and at twenty years after resection there were 10.4 per cent surviving. This table (page 515) gives adequate proof of the curability of favorable types of cancer of the stomach.

The authors have a number of collaborators who help to complete the surgical picture of the disease, emphasizing the current practices and teachings of the Mayo Clinic group with reference to carcinoma of the stomach. Especially valuable chapters are contributed by Snell, Broders, MacCarthy, and Berkson.

The statistical analysis of this material from one clinic constitutes an important contribution to the surgical literature of carcinoma of the stomach.

Skin Grafting. By E. C. Padgett. 149 pp., 87 illustrations. Springfield, Ill., 1942. Charles C Thomas, Publisher. $4.50.

This small monograph by Dr. Padgett is a very welcome and admirable addition to the literature of the subject of transplantation of skin. In eleven well-chosen chapters, the author traces briefly the historical aspects of skin grafting, the important item of homotransplantation, and the histology of grafts, as well as the various types of skin grafts and the problems incidental to the various sites to be grafted and types of grafts employed.

The author's own very important contribution to skin grafting, the dermatome and its use, is well described. Unquestionably, this is one of the best books that has ever been written on the subject of skin grafting. It is recommended enthusiastically to all who concern themselves with this interesting and important phase of surgery.

Diseases of the Thyroid Gland. By Arthur E. Hertzler. 670 pages, with 354 illustrations. New York, 1941, Paul B. Hoeber, Inc. $8.50.

As the author states, this book is a record of his studies of diseases of the thyroid extending over a period of nearly fifty years. There are few doctors who have studied their cases as carefully from the point of diagnosis, pathology, and treatment. One may not agree with the author's ideas concerning the histology of the various diseases of the thyroid gland nor his recommendations for total thyroidectomy; however, for the most part, his ideas of treatment are more or less along the generally accepted lines and the book is an acceptable review of diseases of the thyroid.

There are some objections that might be voiced against a medical book of this type. While "slapstick" humor may be part of one's personality, too much of it in a medical book is not only tiresome but also detracts from the dignity of the volume. Also, in writing a book on a medical subject, one should express himself chiefly as an authority of the medical subject at hand rather than a prophet in matters of religion, politics, or social conduct. When the author makes such

statements as "I have done many thyroidectomies without any sterile sheets"; "the face mask has for its chief purpose to cover the operator's embarrassment at his ignorance of anatomy," one is tempted to remind the author that before the days of aseptic surgery patients often recovered from operations.

The printing and illustrations are excellent; the only flaw in the printing occurs on page 515 in the discussion of "toxic crisis." A workable index is appended.

Wounds and Fractures: A Clinical Guide to Civil and Military Practice. By H. Winnett Orr, M.D., F.A.C.S., Nebraska Orthopedic Hospital. Pp. 227, illustrations 137. Springfield, Ill., 1941, Charles C Thomas, Publisher. $5.00.

In this monograph the author sets forth his ideas concerning the treatment of wounds of the extremities. His method of management of compound injuries of the extremities has become well known and is practiced widely. The text is essentially a digest of the author's own experience. It is in no sense a comprehensive treatise on wound management. Even in the author's own province, the work of V. Bergmann (1874) and F. E. Dennis (1884), the American surgeon, is not mentioned. The latter author treated compound fractures by immobilization in plaster as long ago as 1884, and was then able to record 154 cases without a death from septic infection and 100 cases without a death from any cause. Quite a remarkable achievement. The author gives no attention to the important item of physical factors concerned in the management of infection. Further, there is no account of the use of the sulfonamides in the treatment of infections of the extremities, a rather serious omission.

Nevertheless, this text affords the general surgeon and the *orthopedist* an opportunity to become familiar with the latest comprehensive expression from H. W. Orr on wound management. A useful reference list of his own writings on the subject is appended. The Orr method, in the hands of those familiar with its use, has saved many lives and constitutes an important agency in wound management. The book can be recommended as constituting an excellent summary of Orr's teachings and practice.

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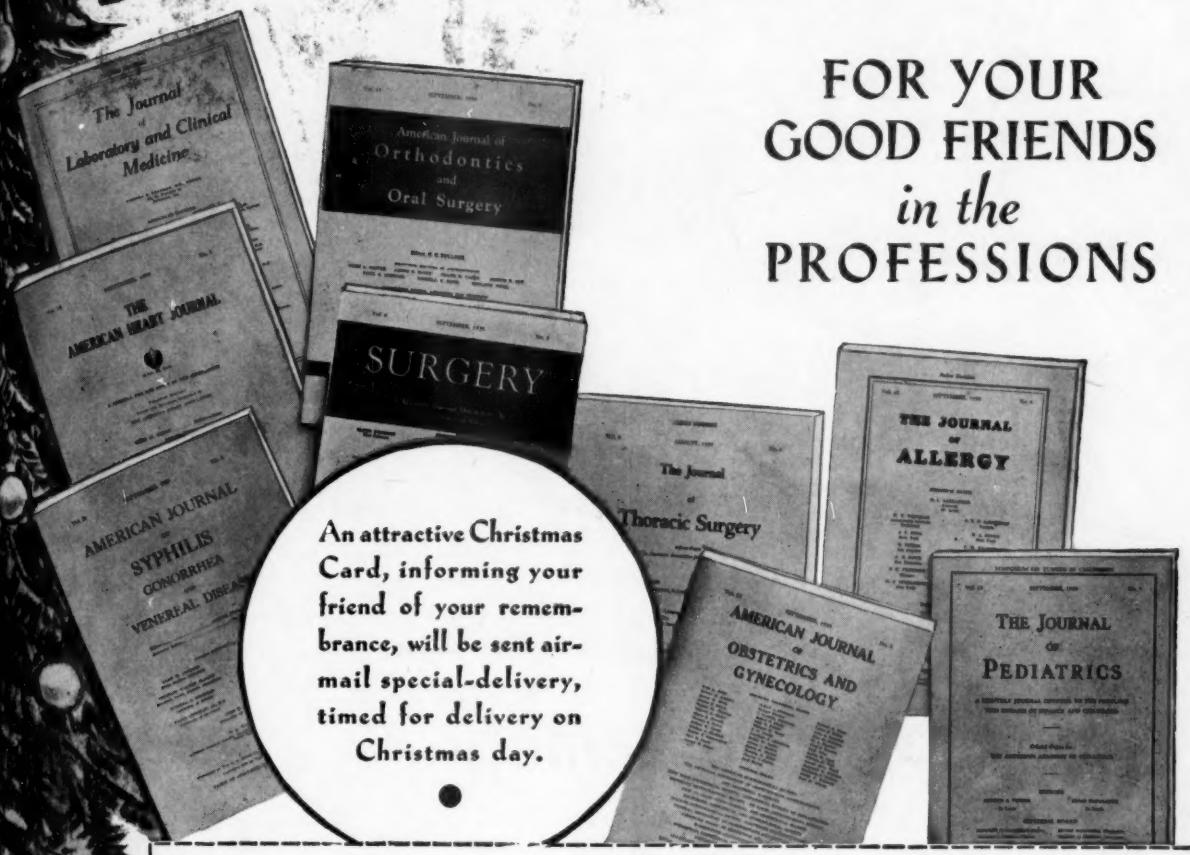
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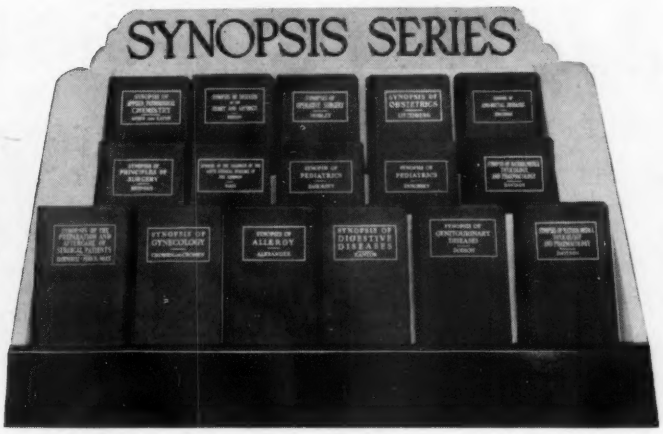

From "THE PLACE OF THE SMALL BOOK IN MEDICINE"

Editorial, Virginia Medical Monthly, June, 1942

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"Worthy of mention in this connection, as examples of the value of small books, are two which have just been published by the C. V. Mosby Company. The first is a Synopsis of Materia Medica, Toxicology and Pharmacology by F. R. Davison, in its second edition. The other, also in its second printing, is a Synopsis of Ano-Rectal Diseases by Louis J. Hirschman. Both books will find a place for themselves."

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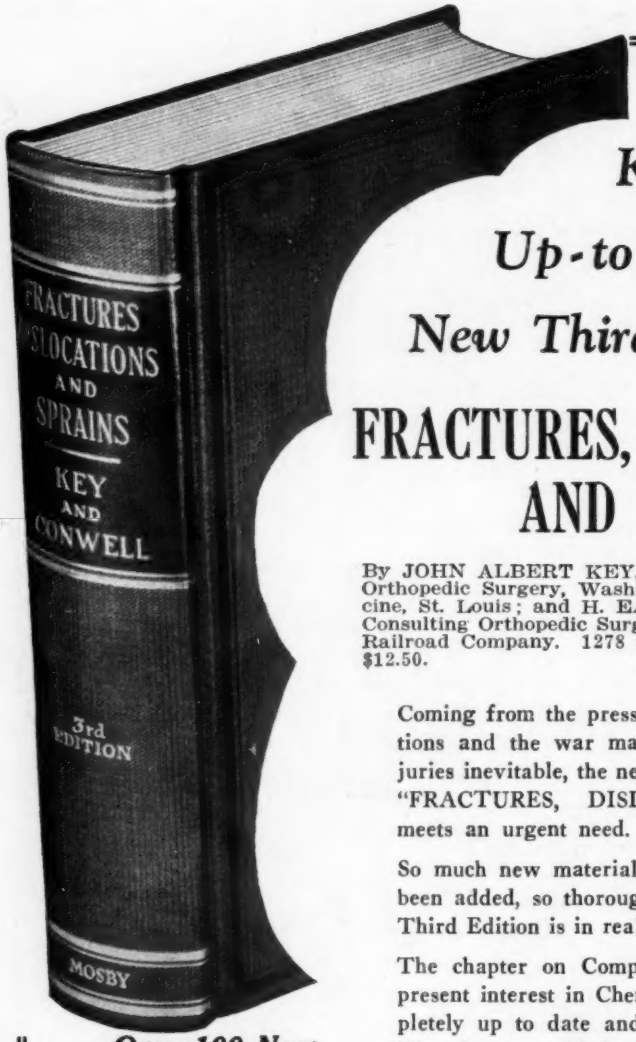

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